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Original Communications

A CLINICOPATHOLOGICAL CLASSIFICATION OF ENDOMETRIAL CARCINOMA BASED ON PHYSICAL FINDINGS, ANATOMICAL EXTENT, AND HISTOLOGICAL GRADE

WILLIAM F. FINN, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology of the Cornell University Medical College and the Woman's Clinic of the New York Hospital)

THERE are many classifications of endometrial carcinoma, none of which has gained universal acceptance. Some divisions are based on clinical findings, others on gross pathological evidence, and still others on the microscopic appearance of the cancer. Despite the fact that panhysterectomy has been the generally preferred treatment for many years, a classification based on surgical and pathological findings has not been developed, standardized, and universally accepted. Cervical carcinoma, in sharp contrast, is divided into either one of two classifications: the League of Nations or the Schmitz. These divisions are universally accepted, even though they are based on clinical evidence alone and even though the specimens obtained by the current revival of surgery reveal errors in staging.

Classifications of Endometrial Carcinoma

Clinical Classifications.—

The classifications of endometrial cancer have been based on clinical findings, gross pathology, or the microscopic picture. Some depend solely on one of these bases, while others have been combinations. Some of the prevalent clinical classifications are:

1. 1929 Heyman[14]
2. 1937 Crossen[7]
3. 1939 Healy and Brown[13]
4. 1940 Miller[20]
5. 1943 Scheffey, Thudium, and Farell[22]
6. 1947 Taylor and Becker[26]

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7. 1949 Palmer, Reinhard, Sadugor, and Goltz[21]
8. 1949 American College of Surgeons[1]

Heyman's[14] classification has 3 parts:

1. Clinically operable,
2. Technically operable, and
3. Inoperable.

Its simplicity recommends it.

Crossen's classification is:

Stage I. Endometrium alone involved.

Stage II. Definite involvement of muscular wall, but not beyond its middle.

Stage III. Extension to the outer half of the uterine wall, but not beyond the borders of the uterus. This includes extension to the peritoneal coat with possible areas of adhesive peritonitis, but without carcinomatous involvement of the adhesions.

Stage IV. Extension to surrounding structures, but not beyond removable ones, such as adnexa and adjacent portions of the broad ligament. There may or may not be extensive intestinal or other peritoneal adhesions, but no extension of carcinoma cells into such adhesions.

Stage V. Extension into structures which it is not advisable to remove, but removal of original tumor is still practicable. The carcinomatous extension may be into an adherent coil of intestine or an adherent area of bladder wall, or it may be along the broad ligament lymphatics into the deep structures of the pelvic wall.

Stage VI. There is such extensive involvement of surrounding structures that not even the main tumor mass can be safely removed.

Crossen's classification is too long, but it distinguishes in an exceptionally lucid manner the various types of extrauterine extension.

Healy and Brown's[13] classification based on the size of the uterus consists of 4 groups:

Group I. Uterus normal in size, depth 3 inches.

Group II. Moderately enlarged uterus, depth 4½ inches, but not larger than a 2½ months' pregnancy.

Group III. Markedly enlarged uterus, 5 inches or more in depth, size of more than 2½ months' pregnancy.

Group IV. Extension of disease beyond the uterus.

Healy and Brown used an easily measured standard, the size of the uterus, but stress its value disproportionately and do not subdivide the extrauterine extensions of carcinoma.

Miller[20] similarly bases his classification on the size of the uterus as follows:

Group I. (Normal.) No palpable enlargment of the uterus, cavity measures 3 inches or less.

Group II. (Moderately enlarged.) Uterus enlarged to 2½ months' pregnancy, cavity measures less than 4½ inches.

Group III. (Markedly enlarged.) Uterus size of 3 months' pregnancy or more, cavity measures more than 5 inches.

This too depends on the size of the uterus which may be a fallible indicator. It also fails to classify extrauterine extension.

Scheffey, Thudium and Farell[22] divide endometrial carcinoma into: (1A) limited to the uterus, and (1B) spread beyond the uterus.

This classification deserves credit because of its simplicity and its basic principle, but it does not adequately distinguish the various types of intrauterine and extrauterine spread of carcinoma.

Taylor and Becker's[26] classification is a slight modification of Healy's. It has 3 groups as follows:

Group I. Those cases in which there is no palpable evidence of uterine enlargement or extension of disease beyond the fundus.

Group II. Those cases showing uterine enlargement without fixation or other evidence of carcinoma elsewhere. This group was subdivided into Group IIA, in which were placed those patients in whom the uterus was larger than a 2½ months' gestation, and Group IIB, which included patients in whom the uterus was not larger than a 2½ months' gestation and still freely movable.

Group III. Patients exhibiting clinical signs of extension of cancer beyond the uterine fundus itself. Group III was further subdivided into those relatively favorable cases in which cancer had extended to the cervix only, and into another group showing evidence of extension beyond the uterus into the vagina, parametria, and adnexa, and distant metastases.

The classification of Palmer and associates[21] is not mutually exclusive and does not divide intrauterine and extrauterine spread in a satisfactory fashion. It is as follows:

Stage I includes those cases in which the disease is confined to the corpus, regardless of the size of the uterus.

Stage II includes those cases where there is extension beyond the corpus to either the cervix, one or both parametria, vagina, and/or distant metastases.

Stage III includes those cases treated elsewhere prior to examination at this institution.

The American College of Surgeons'[1] classification is as follows: (1) primary case, (2) recurrence in vaginal wall after panhysterectomy, (3) local recurrence after panhysterectomy, (4) remote recurrence after panhysterectomy, (5) recurrence after subtotal hysterectomy, and (6) recurrence after irradiation.

This stresses recurrence, the rarer situation, to the detriment of the primary carcinoma, the far more common occurrence.

Gross Pathological Classifications.—

Classifications of endometrial carcinoma based on gross specimens have been made by the following authors:

1. 1919 Ewing[8]
2. 1923 Mahle[18]
3. 1935 Schmitz and Schmitz[23]
4. 1940 Miller[20]
5. 1940 Masson and Gregg[19]
6. 1941 Fricke and Bowing[10]

Ewing's[8] division into circumscribed and diffuse carcinoma has the advantage of simplicity, but it does not consider spread outside of the uterus.

Mahle[18] has classified the progression of endometrial carcinoma on the basis of invasion of the myometrium, thus: (1) microscopic, (2) half the muscle, (3) to serosa, (4) all muscle and serosa.

This grouping is excellent for carcinoma which is confined to the uterus, but it fails to mention extrauterine extension.

The classification of Schmitz and Schmitz[23] follows:

Group I. Growth not greater than 1 cm.

Group II. Growth not greater than 2 to 3 cm.

Group III. Invades more than half the body.
Group IV. Invasion of adjacent structures.

Miller's division[20] into three groups is as follows:

Group I. No carcinoma found or local and/or superficial growth. No deep infiltration.
Group II. More extensive than I and less than III. Not more than halfway through uterine wall.
Group III. Widespread and/or deep infiltration through more than half the uterine wall.
This classification is excellent for intrauterine spread, but once again the extrauterine extensions are not adequately differentiated.

The classification proposed by Masson and Gregg[19] is based on that of Schmitz and Schmitz.[23] It is divided into the following four stages:

Stage I. Limited to endometrium.
Stage II. Muscle coat involved, but peritoneal coat not reached.
Stage III. Peritoneum of uterus involved without gross invasion of other structures.
Stage IV. Any extension outside of the uterus.

This is based on an excellent plan, but the various types of intrauterine and extrauterine extension are not subdivided adequately.

Fricke and Bowing[10] proposed the following stages:

Stage I. Small growth, slight to moderate infiltration of wall, uterus movable.
Stage II. Uterus enlarged: growth infiltrates wall and may or may not infiltrate parametrium.
Stage III. Uterus fixed, parametrial and/or cervical infiltration. Isolated metastases to pelvic lymph nodes or lower vagina.
Stage IV. Uterus enlarged and fixed, metastases to retroperitoneal lymph nodes, ovary, and remote inguinal lymph nodes.
This classification is not clear-cut, overlaps, and mingles indiscriminately the operable and inoperable extensions.

Histological Classifications.—

Histological differentiation has served as the basis for the following classifications:

1. 1911 Kaufmann[16]
2. 1912 Schottlander and Kermauner[24]
3. 1919 Ewing[8a]
4. 1919 Aschoff[2]
5. 1923 Mahle[18]
6. 1927 Lindsay[17]
7. 1930 Healy and Cutler[12]
   1931 Ewing[8b]
8. 1941 Heyman, Reuterwall, and Benner[15]
9. 1943 Scheffey, Thudium, and Farell[22]

These classifications are basically the same inasmuch as their primary division is into a well-differentiated adenocarcinoma, the so-called "adenoma malignum," and a poorly differentiated adenocarcinoma which may be either glandular or solid. Kaufmann's[16] division is: (1) adenoma malignum, (2) adenocarcinoma, (3) papillary adenocarcinoma, (4) solid adenocarcinoma, (5) adenocarcinoma with squamous metaplasia.

The classification of Schottlander and Kermauner[24] is simplicity itself: (1) adenocarcinoma, and (2) primary solid carcinoma.

Ewing's first classification[8a] was as follows: (1) malignant adenoma, (2) papillary adenocarcinoma, (3) alveolar carcinoma, (4) squamous carcinoma.

Aschoff's[2] division is essentially similar: (1) adenoma malignum, (2) adenocarcinoma, (3) solid or medullary carcinoma, (4) squamous-cell carcinoma.

Mahle[18] applied Broders'[3, 4, 5] or histological differentiation to endometrial carcinoma with the following result:

Grade I. Most differentiated carcinoma. Fewer than 25 per cent atypical cells.
Grade II. Twenty-five to 50 per cent undifferentiated cells.
Grade III. Fifty to 75 per cent differentiated cells.
Grade IV. Most undifferentiated carcinoma. More than 75 per cent undifferentiated cells.

Lindsay's[17] classification is into the common adenoma malignum and adenocarcinoma, but he recognizes the rarer adenoacanthoma, adenomyocarcinomatosis, and embryonal carcinoma.

Ewing[8b] later revised his classification to:

Grade I. Superficial papillary adenoma malignum.
Grade II. Adenoma malignum.
Grade III. Adenocarcinoma.
Grade IV. Diffuse anaplastic carcinoma.
Healy and Cutler[12] employed this classification.

The classification of Heyman, Reuterwall, and Benner[15] is as follows:

Group I. Papillary adenocarcinoma.
Group II. Very highly organized and differentiated adenocarcinoma of adenoma malignum type.
Group III. Highly organized and differentiated adenocarcinoma.
Group IV. Less highly organized and differentiated adenocarcinoma up to one-third solid.
Group V. Adenocarcinoma with squamous epithelial areas.
Group VI. Adenocarcinoma of slight organization and differentiation, more than one-third solid.
Group VII. Solid adenocarcinoma without differentiation to squamous epithelium.
Group VIII. Squamous epithelial carcinoma plus solid carcinoma with portions differentiated to squamous epithelium.
Group IX. Uncertain.
Group X. Carcinosarcoma.
Group XI. No microscopic sections.
Group XII. No cancer in sections.
It is too refined to be of practical value.

The classification of Scheffey, Thudium and Farell[22] is: (1) low grade, (2) intermediate grade, (3) high grade, (4) adenoacanthoma, (5) unclassified.

Their low grade corresponds to the first two grades of Ewing, their intermediate grade is the same as Ewing's[8b] Grade 3, while their high grade is equivalent to Ewing's Grade 4. A classification which is based on only two grades such as that of Schottlander and Kermauner[24] and Lindsay[17] does not subdivide the various grades adequately, while a four-grade classification as used by Ewing[8] and Mahle[18] seems to overrefine the problem. Hence, a three-grade classification such as Scheffey[22] employed at the suggestion of Crawford, appears to divide endometrial carcinomas into distinct homogenous groups.

Proposed Clinical Pathological Classification

The inadequacies and defects of the existing classifications, as well as their concentration on either the clinical or pathological aspect to the exclusion of the other, have led to the review of all patients with endometrial carcinoma at the New York Hospital. An attempt to classify these patients by the various classifications described above led to the realization of the deficiencies of the existing groupings. Two hundred ninety-two patients with carcinoma of the endometrium were treated at the Woman's Clinic of the New York Hospital from 1933 through 1950. Curettage specimens were obtained from all, while the uterus, cervix, and both tubes and ovaries were available in the 245 patients who were treated by hysterectomy. Curettage specimens only were available in the other 47 patients who were either not treated or treated only by irradiation. These specimens have been studied (1) to determine their clinical types, their anatomical extent, and their histological grade, (2) to develop a clinical and pathological classification, and (3) to demonstrate its influence on survival.

A clinical division which is based upon physical examination alone is unreliable. It must be based on the accurate delineation of extension which in most cases can be best obtained at the time of operation, even though complete extirpative surgery cannot be performed. A simple clinical classification is:

1. Operable
2. Inoperable
   a. Surgical contraindications
   b. Medical contraindications

This is a modification of Heyman's[14] classification. Operability is a relative term, but as used here means the complete removal of endometrial carcinoma by total hysterectomy and bilateral salpingo-oophorectomy without removal of bladder or ureters. The horizons of operability are being extended by Brunschwig[6] and others. A carcinoma which can be completely removed by hysterectomy, cystectomy, or abdominal-perineal resection of ureters may soon be considered operable, but the stricter definition, because of its more general applicability, serves for the present. Inoperability may be based on medical contraindications such as age, obesity, cardiac or renal disease. The extension revealed by physical examination or at operation may decide the issue.

The 292 patients at the New York Hospital were classified on a clinical basis as shown in Table I. Surgical inoperability was determined by pelvic palpation, by x-ray evidence of distant metastases, and by exploratory laparotomy. The chief radical contraindication was heart disease in 14 patients. This consisted of severe hypertensive disease in 6, congestive failure in 3, fibrillation in 2, advanced rheumatic heart disease in 2, and one patient with a recent coronary occlusion. Extreme obesity precluded operation in 3 patients. Age in one, carcinoma of the bronchus in another patient, and carcinoma of the breast with axillary metastases led to the decision not to operate on the last patient.

TABLE I. CLASSIFICATION OF ENDOMETRIAL CARCINOMA BASED ON CLINICAL FINDINGS

DIVISION		NUMBER		PER CENT
Operable		245		83.9
Inoperable		47		16.1
Surgical	27		9.3	
Medical	20		6.8	
Total		292		100.0

Clinical classification at best is only suggestive, and for accuracy must be associated with a pathological classification. Carcinomas of the uterus have

been classified by their size. Healy,[13] Miller,[20] and others feel that a uterus of normal size indicates an early carcinoma, while the converse is true for an enlarged uterus. This division is, in general, sound, but the reliance on the size of the uterus fails to consider enlargement of the uterus by myomas, hypertrophy of the myometrium and adenomyosis. An enlarged uterus may contain a carcinoma which is limited to the endometrium while a uterus of normal size may be accompanied by an advanced endometrial carcinoma which has progressed even beyond the uterus.

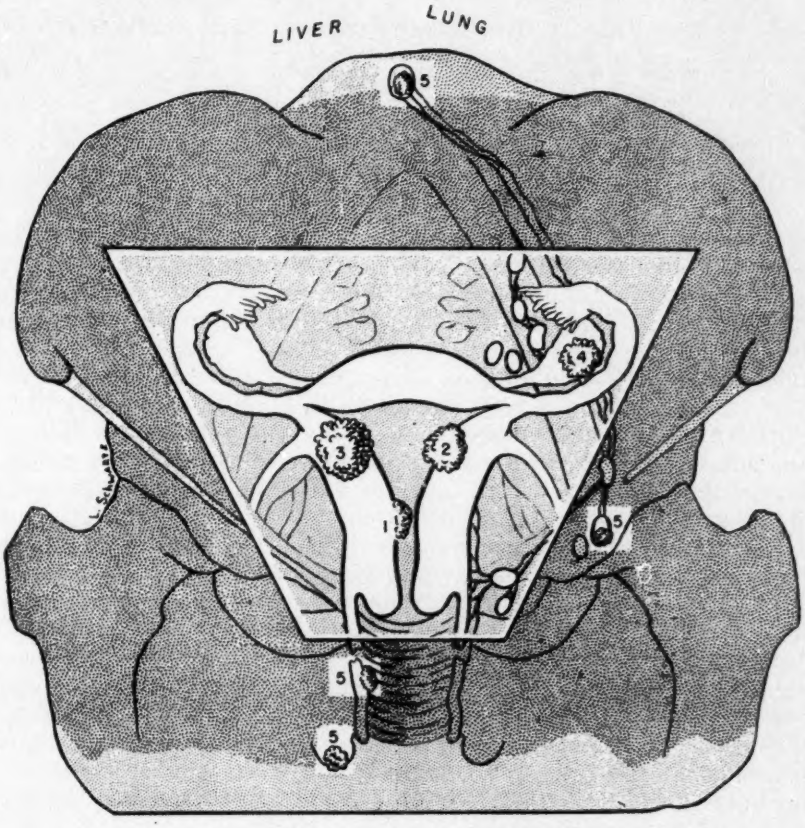

Fig. 1.—The anatomical stages of endometrial carcinoma.

A classification of the anatomical extent based primarily on gross and microscopic examination supplemented by observations at laparotomy, x-ray investigations, and other laboratory methods is as follows (Fig. 1):

Stage 1 includes carcinoma confined to the endometrium.
Stage 2 shows penetration of the superficial millimeters of the myometrium.
Stage 3 shows penetration of the deeper layers of the myometrium.
Stage 4 includes penetration of the uterine serosa and metastases to tubes, ovaries, round or broad ligaments, and pelvic lymph nodes.
Stage 5 denotes the presence of extrapelvic metastases (vagina, vulva, para-aortic lymph nodes, lungs, or other distant organs).

The microscopic sections may reveal extension which is not evident grossly. Table II shows the distribution of endometrial carcinomas by anatomical extent.

Classifications which are based on gross or microscopic evidences of anatomical extent are far more accurate, but since Mahle[18] in 1923 adapted

TABLE II. CLASSIFICATION OF ENDOMETRIAL CARCINOMA BASED ON ANATOMICAL EXTENT

STAGE	NUMBER	PER CENT
1. Endometrium	115	39
2. Superficial myometrium	69	23
3. Deep myometrium	31	11
4. Pelvic organs or nodes	46	16
5. Extrapelvic sites	31	11
Total	292	100

TABLE III. CLASSIFICATION OF ENDOMETRIAL CARCINOMA BASED ON HISTOLOGICAL GRADE

GRADE	NUMBER	PER CENT
A. Well differentiated	155	53
B. Intermediate	62	21
C. Poorly differentiated	75	26
Total	292	100

Broder's[3, 4, 5] classification of histological differentiation to endometrial carcinoma, cancers of the endometrium have usually been divided into four histological grades. Grade A represents the cancer which most closely resembles the cells of the normal endometrium. They have fewer than 25 per cent undifferentiated cells. Grade D shows the most extreme variation from the normal endometrial pattern. It exhibits over 75 per cent undifferentiated cells. Grades B and C are intermediate grades which show 25 to 50 per cent and 50 to 75 per cent undifferentiated cells, respectively. This classification is based on the number of anaplastic and mitotic cells. The differences between grades B and C are not so outstanding that uniformity of opinion exists. Competent pathologists will disagree on these borderline specimens. Accordingly, it seems better to have only three histological grades as Scheffey[22] advocates. These grades are based on the pattern of the acinar arrangement as well as on the characteristics of the individual cell. Grade A is the well-differentiated carcinoma with preservation of a glandular pattern with little mitotic activity and few characteristics of anaplasia (Fig. 2). Grade B is the intermediate carcinoma with more anaplasia and mitoses and with some loss of the glandular pattern (Fig. 3). Grade C is the most undifferentiated carcinoma with little preservation of an acinar pattern (Fig. 4). It grows in solid plaques of cells with marked anaplasia and a high degree of mitotic activity. Grades A and C are readily recognized. The remaining specimens fall into Grade B. Table III shows the distribution of histological grades observed at the New York Hospital.

TABLE IV. CORRELATION OF CLASSIFICATIONS

		ANATOMICAL STAGES					HISTOLOGICAL GRADES		
CLINICAL		*1*	*2*	*3*	*4*	*5*	A	B	C
Operable	245	100	69	31	45	0	142	51	52
Surgically inoperable	27	0	0	0	1	26	2	8	17
Medically inoperable	20	15	0	0	0	5	11	3	6
Total	292	115	69	31	46	31	155	62	75

The inadequacy of the present classifications of endometrial carcinoma demonstrates the need for a classification which is based on both gross and microscopic pathology as well as clinical findings. The correlation of the various classifications is demonstrated in Table IV. As would be expected, any degree of anatomical extent or histological grade may occur in a carcinoma which is inoperable because of medical contraindications. The anatomical extent in

these circumstances is based on physical examination only and hence is not as reliable as when determined by operation or gross pathological examination. However, the clinical impression has been confirmed by postmortem examination in 8 of the 20 patients who were inoperable because of medical reasons. There is a close correlation between the clinical and the anatomical classifications.

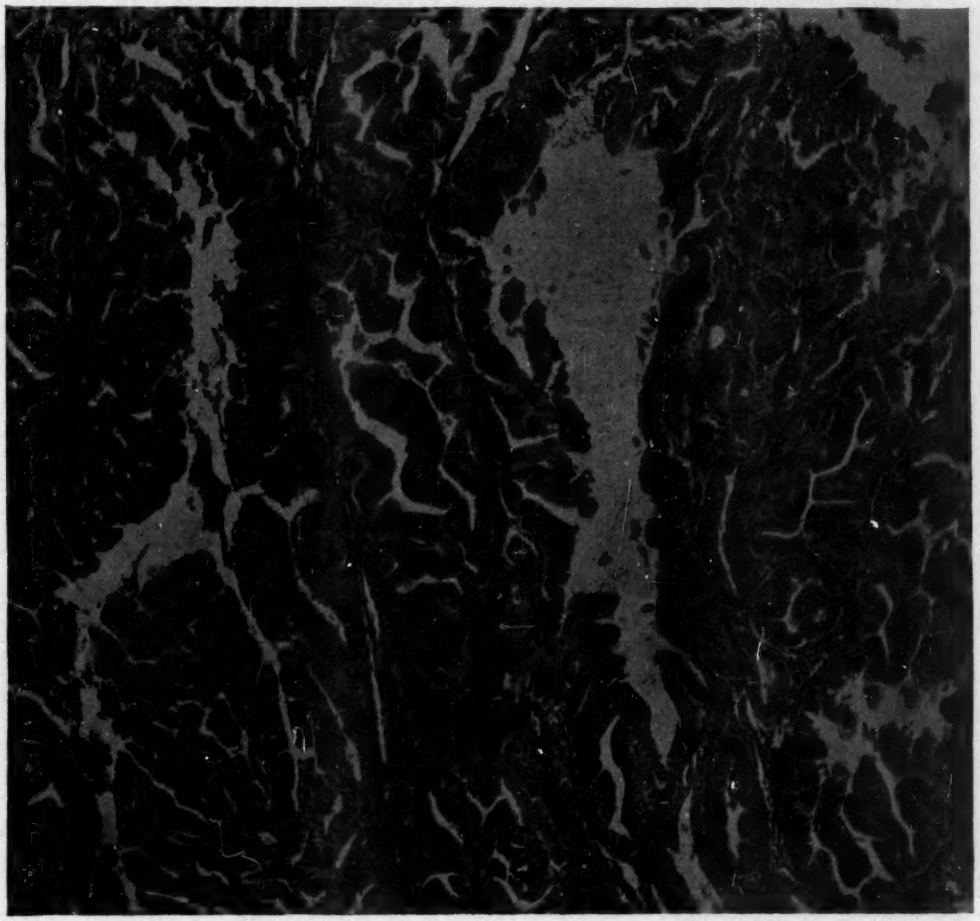

Fig. 2.—Grade A, the lowest grade of malignancy. Note the well-preserved acinar pattern.

Anatomical Stages 1, 2, and 3, and most of 4 correspond to the operable cases, while an occasional Stage 4 and all Stage 5 cases are inoperable. There is a relatively close correlation between the anatomical extent and the histological grade as shown in Table V. It is readily evident that 132 (82 per cent) of Grade A cancers were limited to Stages 1 and 2, while 29 (49 per cent) of Grade B and 23 (31 per cent) of Grade C were so limited. Conversely only 23 (15 per cent) of Grade A carcinomas extend to Stages 3, 4, and 5, while 33 (53 per cent) of Grade B and 52 (69 per cent) of Grade C showed Stages 3, 4, and 5 involvement. Even carcinoma of histological Grade A may extend to Stages 3, 4, and 5 if enough time is allowed to elapse between the appearance of symptoms and treatment. Similarly carcinoma of Grade C may be confined to the endometrium or superficial myometrium (Stages 1 and 2), if it is detected early enough. The correlation between the clinical divisions and the histological

grades is less constant than between the clinical divisions and the anatomical stages or between stages and grades. In general, the carcinomas which are surgically inoperable are of the highest grade of histological malignancy.

An adequate classification would include clinical, gross pathological, and histological evidence. Thus, an endometrial carcinoma may be operable, confined to the endometrium, and of the lowest grade of histological malignancy. This could be abbreviated to Operable 1A. If the carcinoma is inoperable be-

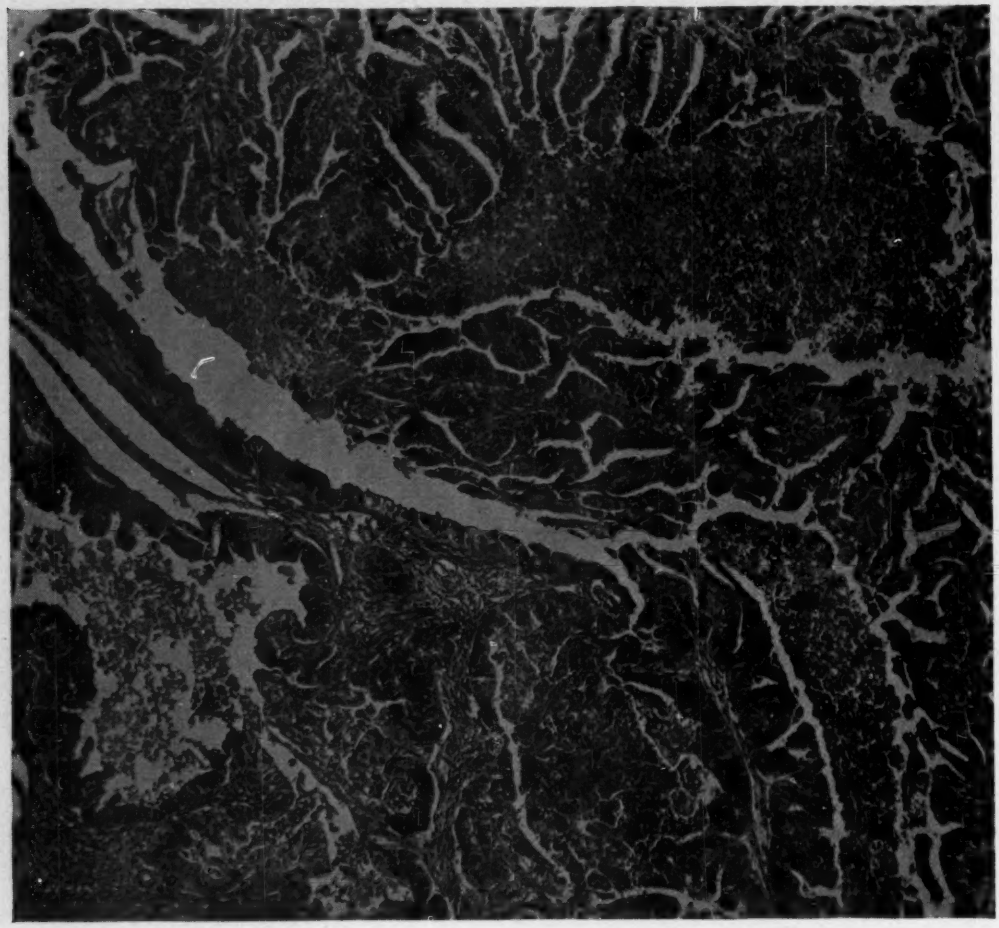

Fig. 3.—Grade B, the intermediate grade of malignancy. Note the increasing disorder and anaplasia.

cause of its extension outside of the pelvis and curettage alone was performed revealing the highest degree of histological malignancy, it could be classified in synoptic fashion thus: Inoperable (S) 5C. If only curettage and irradiation were performed because of medical contraindications, but the carcinoma appeared to be confined to the uterus by physical examination, and curettage revealed an intermediate grade of malignancy, this concept could be expressed thus: Inoperable (M) 1B. The stage could not be stated with certainty because its determination depended on physical examination alone. Curettage can reveal only a tentative histological grade because of the possible inadequacy of sampling. Inasmuch as the vast majority are operable, the classification can be abbreviated into stage and grade; for example, 1A or 4B.

The frequency and time of recurrences as demonstrated elsewhere[9] bear a direct ratio to both the anatomical stage and the histological grade. Stage 1 had a recurrence rate of 10 per cent and an average time of recurrence of 2.2 years, Stage 5 showed 62 per cent recurrence and an average time of recurrence of 0.5 years. Eight per cent of the patients with Grade A malignancy had

Fig. 4.—Grade C, the highest grade of malignancy. Note the advanced anaplasia and complete loss of acinar pattern.

recurrences. Forty-four per cent of patients with Grade C malignancy had recurrences. The average was 2.3 and 1 year, respectively. Survival time by clinical division, anatomical extent, and histological grade is outlined in Table VI. Operability resulted in a survival time which was three and one-half

TABLE V. CORRELATION BETWEEN EXTENT AND GRADE

ANATOMICAL EXTENT	HISTOLOGICAL GRADE					
	A		B		C	
	NUMBER	%	NUMBER	%	NUMBER	%
1	97	63	10	16	8	11
2	35	22	19	31	15	20
3	12	8	10	16	9	12
4	9	6	14	22	23	30
5	2	1	9	15	20	27
Total	155	100	62	100	75	100

times better than when operation was not possible. Patients with the first four stages of anatomical extent have approximately the same survival time. This averages about 6.5 years, which is 3.5 times better than the expectancy of patients with Stage 5. This survival time also reflects the completeness of surgical extirpation in the first 4 stages and the incompleteness of treatment when the carcinoma has extended outside of the pelvis. Survival time is approximately 1.5 times as good for patients with Grades A and B as for patients with Grade C.

TABLE VI. SURVIVAL IN YEARS

CLINICAL		ANATOMICAL		HISTOLOGICAL	
Operable	6.5	Stage 1	6.0	Grade A	4.8
		2	6.7		
		3	5.5	B	6.3
		4	7.0		
		5	1.8	C	3.8
Inoperable	1.8				

Discussion

The incompleteness of the present classifications of carcinoma has led to the proposal of a clinical-pathological classification. This is based on three factors: first, the clinical distinction of operability and inoperability, second, the pathological determination of anatomical extent, and third, the histological grade. A classification which is based on clinical evidence alone contains an irreducible amount of error, even when it is based on sound principles of division.

Most gross pathological classifications place too much stress on the size of the uterus. While the uterine enlargement indicates the extent of the carcinoma to some degree, it is not accurate. Glaring exceptions exist. As more radical surgery is performed, extrauterine extensions must be listed, but most pathological classifications fail to consider them. The anatomical extent determines the operability and is, in consequence, more important than microscopic grading.

The disparity between the curettage specimen and the entire endometrium reveals the inaccuracy of grading. This difficulty is readily obviated by refusal to place more than a tentative grade on a curettage specimen. If, however, the curettage reveals the highest degree of malignancy, it may be diagnosed Grade C, but a final statement regarding the lesser grades of malignancy should be made only after the entire endometrium has been examined.

The term "adenoma malignum" creates a problem. Contrary to the original usage of Gusserow,[11] who first employed the phrase in 1870, and Selberg,[25] it now connotes to some not the earliest form of carcinoma, but a precancerous change. Ewing[8a] has perpetuated its use, but employed it to designate the two earliest forms of carcinoma; the papillary adenoma malignum and the diffuse adenoma malignum. The diagnosis of "adenoma malignum" should not be applied to curettings, since the sample may not be representative. Its apparent contradiction in terms can only continue to confuse pathologists and it had best be called what it actually is, adenocarcinoma of a low grade of malignancy, or Grade A adenocarcinoma.

The definition of operability—complete removal of carcinoma by total hysterectomy and bilateral salpingo-oophorectomy—is tentative and has been selected as being most suitable to current surgical practice. It does not attempt to deny the operability of an extension to a pelvic lymph node which can be removed by lymph node dissection. Nor does it imply that extension to the bladder or rectum, which can be completely extirpated by pelvic exenteration, is inoperable. Conversely, it does not mean that the mere performance of total hysterectomy and bilateral salpingo-oophorectomy means operability, if extrauterine extension remains. The clinical division of operability includes the

anatomical stages 1, 2, 3, and most of 4. Stage 4 extrauterine spread to the parametrium, the serosa of the uterus, the round ligament, the tube and ovary can be completely removed by hysterectomy. The vast majority of Stage 4 carcinomas are operable and only the occasional case of Stage 4 extrauterine intrapelvic extension is inoperable.

This clinical-pathological classification has been devised for endometrial carcinoma but it applies with minor changes to endometrial sarcoma, myometrial sarcoma, carcinoma of the cervix, and carcinoma of the ovary.

In view of the present unsatisfactory classification of endometrial carcinoma, it is suggested that the interested national societies devise a classification which is worthy of universal adoption and use.

Summary

The current classifications of endometrial carcinoma have been analyzed. Their inadequacy and lack of universal acceptance have led to the development of a clinical-pathological classification which is based on a combination of the clinical division, the pathological stage, and the microscopic grade. The clinical division is based on operability. The current standard includes the complete removal of all carcinoma by total hysterectomy and bilateral salpingo-oophorectomy.

The size of the uterus has been criticized as a basis for classification.

Classification based on the anatomical extent of the carcinoma as determined by gross and microscopic examination has been substituted and is as follows:

Stage 1, confined to endometrium.
Stage 2, involvement of superficial myometrium.
Stage 3, penetration of deep myometrium.
Stage 4, intrapelvic extension exclusive of bladder and rectum.
Stage 5, extrapelvic extension.

The use of four histological grades is overrefined. A histological classification which is based on three grades follows:

Grade A, well differentiated.
Grade B, intermediate.
Grade C, poorly differentiated.

It has been suggested that the term "adenoma malignum" be abandoned. This lesion should be called what it actually is—well-differentiated or Grade A adenocarcinoma of the endometrium.

There is a close correlation between the clinical divisions and the anatomical stages. The anatomical stages parallel the histological grades. The connection between the clinical divisions and the histological grades is less intimate. The anatomical extent with its consequent operability is more important than the histological grade. Both the incidence of recurrences and the survival time bear a direct relationship to the operability, to the anatomical extent, and to the histological grade of the endometrial carcinoma.

An abbreviated method of expressing classification has been suggested. Since the vast majority of endometrial carcinomas are operable, the clinical

division of operability may be omitted. The carcinoma is then accurately classified by its anatomical stage and histological grade, e.g., 1A, 2B, or 5C.

It is suggested that national gynecological or cancer societies formulate an adequate clinicopathological classification of endometrial carcinoma which by its universal adoption would result in a uniform, generally accepted classification.

References

1. American College of Surgeons: Personal communication, 1949.
2. Aschoff, L.: Pathologische Anatomie, Jena 1919, Fischer, Vol. II, p. 666.
3. Broders, A. C.: J.A.M.A. **74**: 656, 1920.
4. Broders, A. C.: Ann. Surg. **73**: 141, 1921.
5. Broders, A. C.: Ann. Surg. **75**: 574, 1922.
6. Brunschwig, A.: Cancer **1**: 177, 1948.
7. Crossen, H. C.: Am. J. Obst. & Gynec. **33**: 587, 1937.
8. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company; (a) ed. 1, 1919, (b) ed. 3, 1931.
9. Finn, W. F.: Am. J. Obst. & Gynec. **60**: 773, 1950.
10. Fricke, R. E., and Bowing, H. H.: Am. J. Roentgenol. **46**: 683, 1941.
11. Gusserow, A. L.: Arch. f. Gynak. **1**: 239, 1870.
12. Healy, W. P., and Cutler, M.: Am. J. Obst. & Gynec. **19**: 457, 1930.
13. Healy, W. P., and Brown, R. L.: Am. J. Obst. & Gynec. **38**: 1, 1939.
14. Heyman, J.: Proc. Roy. Soc. Med. **22**: 801, 1929.
15. Heyman, J., Reuterwall, O., and Benner, S.: Acta Radiol. **22**: 11, 1941.
16. Kaufmann, E.: Specielle Pathologische Anatomie, Berlin, 1911, Reimer, Vol. 2, p. 1030.
17. Lindsay, W. S.: Surg., Gynec. & Obst. **44**: 646, 1927.
18. Mahle, A. E.: Surg., Gynec. & Obst. **36**: 385, 1923.
19. Masson, J. C., and Gregg, R. O.: Surg., Gynec. & Obst. **70**: 1083, 1940.
20. Miller, N. F.: Am. J. Obst. & Gynec. **40**: 791, 1940.
21. Palmer, J. P., Reinhard, M. C., Sadugor, M. C., and Goltz, H. L.: Am. J. Obst. & Gynec. **58**: 457, 1949.
22. Scheffey, L. C., Thudium, W. J., and Farell, I. M.: Am. J. Obst. & Gynec. **46**: 786, 1943.
23. Schmitz, H., and Schmitz, H. E.: Am. J. Roentgenol. **34**: 759, 1935.
24. Schottlander, J., and Kermauner, F.: Zur Kenntnis des Uteruskarzinoms, monographische Studie uber Morphologie, Entwicklung, Wachstum, nebst Beitragen zur Klinik der Erkrankung, Berlin, 1912, S. Karger.
25. Selberg, F.: Arch. f. path. Anat. **160**: 552, 1900.
26. Taylor, H. C., Jr., and Becker, W. F.: Surg., Gynec. & Obst. **84**: 129, 1947.

57 West 57th Street.

THE ADVANTAGES TO MOTHER AND INFANT OF AMPHETAMINE IN OBSTETRICAL ANALGESIA*†

STUART ABEL, M.D., F.A.C.S., ZELDA B. BALL, PH.D., AND S. C. HARRIS, PH.D.,
CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University Medical School, and the Department of Physiology and Pharmacology, Northwestern University Dental School)

THE ideal medication for analgesia during labor must possess two important qualities; namely, adequate analgesic properties for the mother and minimal respiratory hazard to the baby. The role of epinephrine and epinephrine-like compounds in the production and potentiation of analgesia has been established.[2-13] Amphetamine (Benzedrine, in particular) is one of the compounds like epinephrine which has been found both experimentally and clinically to potentiate analgesia. Another important pharmacological property of amphetamine is the respiratory stimulating effect of the drug.[14-18]

The rationale for adding amphetamine to morphine in obstetrical analgesia, therefore, is the potentiating effect of amphetamine on morphine analgesia, the respiratory stimulating effect to counteract the morphine depression of the respiration of the newborn, and also the possibility of producing euphoria in the parturient woman.

Our clinical experience with the morphine-amphetamine combination was preceded by laboratory studies on dogs.[11] When amphetamine and morphine were given to pregnant bitches, delivered by section, the amphetamine markedly counteracted the depressing effect of morphine on the newborn, premature puppies. These pups showed excellent muscle tone, and were extremely responsive to external stimuli. The pups born of mothers given larger doses of amphetamine displayed a reaction resembling opisthotonos, when their feet were snapped. A comparable reaction has been noted in the human babies whose mothers were similarly overmedicated.

Clinical Material and Method

After these preliminary animal studies we began to accumulate clinical information when the morphine-amphetamine combination was used during labor. We have attempted to evaluate the clinical worth of this combination by comparing the patients and infants after morphine-amphetamine with patients and infants after other types of medication, with particular reference to the respiratory status of the newborn infant. To date data from seven thousand cases from the Passavant Memorial and Wesley Memorial Hospitals have been analyzed. This is primarily concerned with the influence of amphetamine on the newborn infant. Because of the subjective nature of analgesia and the inherent difficulties of its objective evaluation, no critical study of maternal analgesia was made, although the clinical impression is favorable.

The following information was recorded by the anesthesiology departments of the participating hospitals on special sheets supplied for this purpose.

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†Aided in part by a grant from the Smith, Kline & French Laboratories.

1. The date and hospital number for identification of cases.

2. The dose and time of administration of all drugs given during labor,* and the time of delivery. (The time lapse between administration of medication and delivery is henceforth referred to as the "Rx" interval.)

3. The type of delivery with pertinent information relative to variations from the normal.

4. The type, duration, and depth of the anesthetic agent used.

5. The (stop-watch) interval between delivery of the chin and the first respiration. (Henceforth referred to as the "C-R" interval.)

6. Any special attention required to resuscitate the baby (oxygen, etc.).

To reduce the factors which might conceivably affect the baby's respiratory incentive, obstetrical variables were considered and the following cases were excluded: cesarean section, breech presentation, twin pregnancy, premature and immature babies (under 5 pounds), placenta previa and abruptio placentae, and any cases in which evidence of toxemia was manifested.

Amphetamine sulfate is the official U.S.P. nonproprietary name for the drug under study. Benzedrine† (dl-amphetamine) is a racemic mixture of two optical isomers, Dexedrine† or d-amphetamine and Levadrine or l-amphetamine. The dextrorotatory isomer is the more active one and as a consequence Dexedrine has come to be used more frequently than Benzedrine.

For this presentation we have selected four types of cases for study:

1. Those patients given $\frac{1}{6}$ gr. of morphine sulfate.
2. Those given $\frac{1}{6}$ gr. of morphine sulfate plus 5 mg. of d-amphetamine or 10 mg. of dl-amphetamine.
3. Those given 100 mg. of Demerol and $\frac{1}{150}$ grain of scopolamine.
4. Those who received no analgesic drug as a control.

The cases were not selected for any particular type of medication. All drugs were administered intramuscularly. The Demerol-scopolamine is included for comparison because of its widespread popularity in clinical obstetrics.

It was immediately apparent that many of the mothers were stimulated after the joint medication (in the same syringe) of $\frac{1}{6}$ gr. of morphine and 10 mg. of dl-amphetamine. Since this effect was not desired we subsequently injected the amphetamine 20 minutes after the morphine.

It became obvious as the data accumulated that the drug influence on the C-R interval was masked by the kind and depth of inhalation "analgesic-anesthetic" used prior to delivery. It then became necessary to find a method for evaluating the specific influence of the anesthetic. A large series of cases was tabulated in which no analgesic drug was administered. This so-called control series was divided into the following groups:

1. Those patients receiving cyclopropane or nitrous-oxide analgesia only.
2. Those receiving cyclopropane anesthesia without preceding gas analgesia.
3. Those receiving cyclopropane or nitrous-oxide analgesia followed by cyclopropane anesthesia.

The number of cases in Group 1 did not permit a critical evaluation of the influence of the gas analgesia, but it appeared to have little or no effect on the C-R interval.

Group 2 was studied and found to yield a very high correlation‡ between the duration of anesthesia and the C-R interval.

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*Drug medication discussed later in text.

†Smith, Kline & French Laboratories generously supplied the 10 mg. ampules of Benzedrine sulfate and 5 mg. ampules of Dexedrine sulfate used in this study.

‡Coefficient of correlation (r) 0.551. This means that there is much less than one chance in one hundred that such a relationship would occur by chance.

The same relationship* was found in Group 3 in cases where the cyclopropane anesthesia was preceded by inhalation analgesia. Further, since there was no significant difference between the means of Groups 2 and 3, it became possible to pool them.

Since the pooled data demonstrate a marked linear relationship† it was possible to calculate a regression coefficient "b."‡ In this case the coefficient of regression is the average C-R increment in seconds per minute of cyclopropane anesthesia and it was found that each minute of cyclopropane anesthesia, up to eighteen minutes, increases the C-R by 3.26 seconds.

The regression equation is depicted as the straight line in Fig. 1. The average C-R for each minute of gas anesthesia is represented by the circles and the number within the circles represents the actual number of cases included in these averages. The number within the zero anesthesia circle represents the cases which had inhalation analgesia but no anesthesia. These latter cases were not used to obtain the regression coefficient, but were included to establish the ultimate control average of 30.3 seconds.

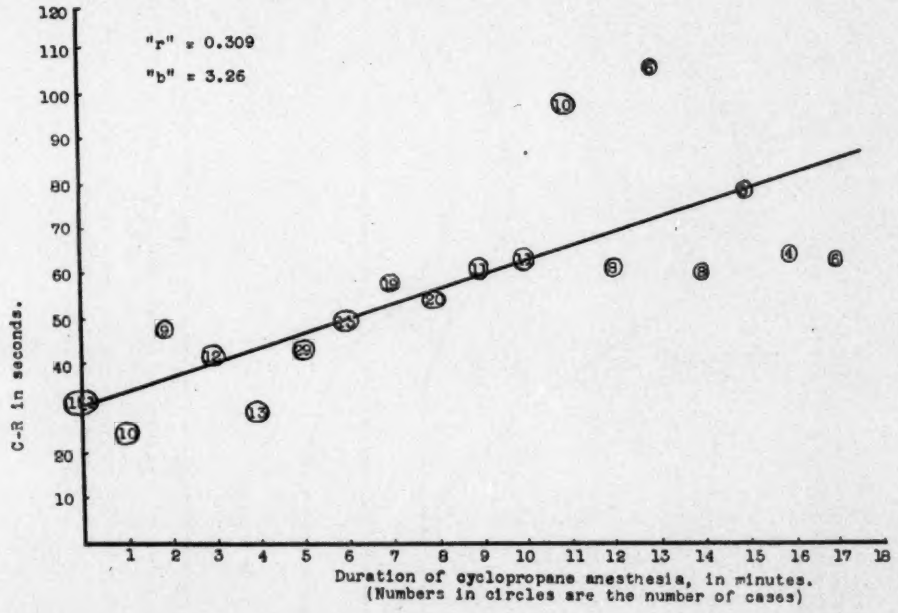

Fig. 1.—Influence of maternal cyclopropane anesthesia on the respiratory incentive of the newborn.

After establishment of a factor to minimize or eliminate the influence of the anesthetic, it became possible to study the influence of the analgesic on the infants' respiratory incentive. The regression coefficient (3.26 sec./min.) was applied to all cases, in other words 3.26 seconds was subtracted from the C-R interval of each individual case for each minute of cyclopropane anesthesia given to the mother. For example, if the mother were anesthetized for 3 minutes and the C-R interval for the infant were 35 seconds, 9.78 seconds (3 × 3.26) were subtracted so that the C-R interval was corrected to 25 seconds.

*Coefficient of correlation (r) 0.286. This value also falls beyond the 1 per cent level, or in other words there is less than one chance in one hundred that this relationship would occur by chance.

†Coefficient of correlation (r) 0.309. This value for 199 cases means that there is less than one chance in one hundred that this correlation is due to chance.

‡Coefficient of regression "b," the rate of change of the dependent variable upon the independent variable, i.e., the slope.

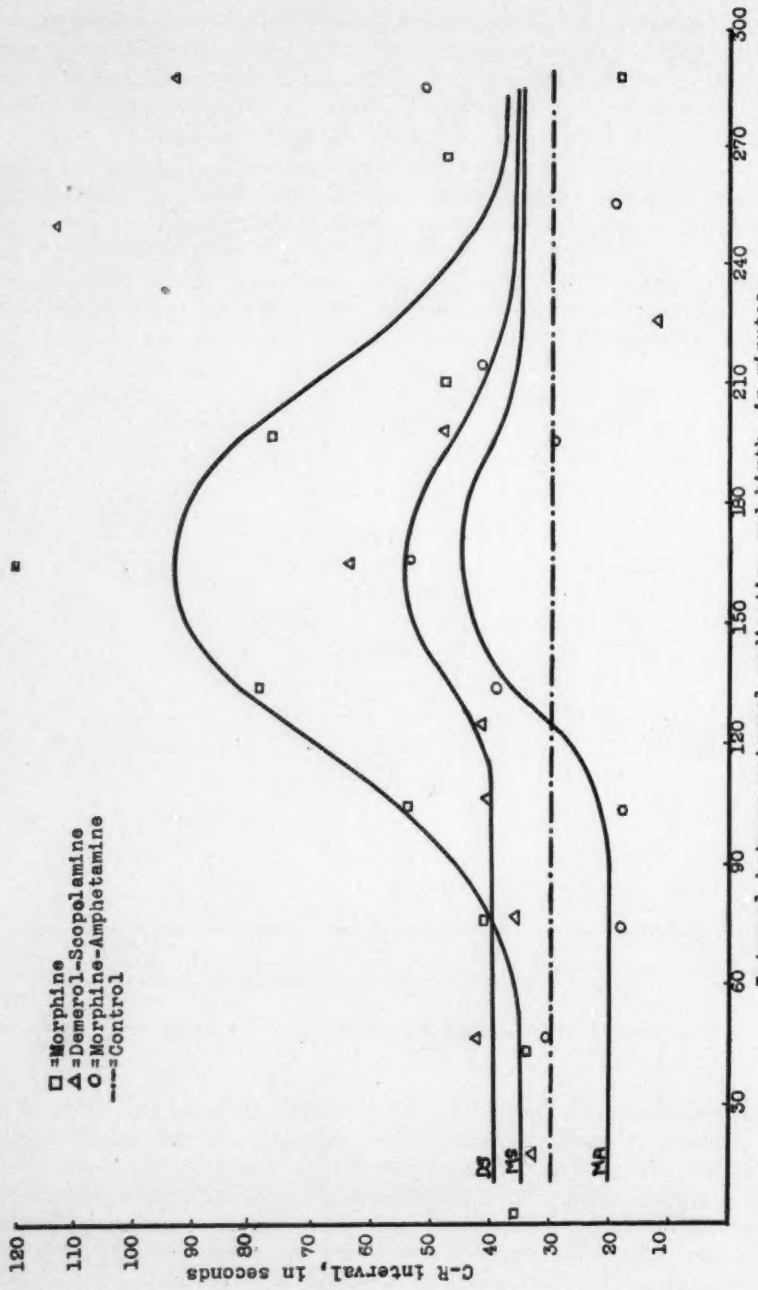

Fig. 2.—Graphic comparison of the influence of maternal medication and the interval between maternal medication and birth on the respiratory incentive of the newborn.

Results

All of the data to be compared are presented in Table I. For each of the four groups the following information is given: The first column is devoted to arbitrary 30-minute divisions of the Rx interval (time lapse between the administration of the analgesic drug and the time of birth). The second column, labeled "Average Rx," gives the average Rx intervals obtained from the cases occurring within the 30-minute periods. The third column, entitled "Average Antepartum Anesthesia," presents the average number of minutes of cyclopropane anesthesia given the mothers in each Rx group. The column titled "n" gives the number of cases comprising each segment of the sample. The column headed by the term "Newborn Average C-R" is divided to give the actual C-R average (the average time lapse between delivery of the chin and the first respiration) for each Rx group, and the corrected C-R average.

TABLE I. COMPARISON OF THE INFLUENCE OF MATERNAL MEDICATION AND THE INTERVAL BETWEEN MATERIAL MEDICATION AND BIRTH ON THE RESPIRATORY INCENTIVE OF THE NEWBORN

MEDICATION	RX RANGE (MIN.)	AVERAGE RX INTERVAL (MIN.)	AVERAGE ANTEPARTUM ANESTHESIA (MIN.)	N	NEWBORN AVERAGE C-R	
					UNCORRECTED (C-R)	CORRECTED (C-R)
None*	0	0	4.98	350	44.3	31.9
Morphine sulfate, grain 1/6	1–30	6.0	11.0	1	72.0	36.0
	31–60	43.3	4.4	7	48.0	33.8
	61–90	78.4	6.6	5	66.0	40.6
	91–120	103.7	4.0	3	66.7	53.7
	121–150	133.4	8.7	7	107.7	78.7
	151–180	164.0	12.3	4	151.3	120.0
	181–210	196.0	8.8	4	105.0	76.5
	211–240	211.0	13.0	1	90.0	48.0
	241–270	265.0	11.0	3	83.3	47.3
	271–300	289.0	9.0	3	47.3	18.0
				38		
Morphine sulfate, grain 1/6 plus 5 mg. d-amphetamine or 10 mg. dl-amphetamine	1–30			0		
	31–60	48.6	5.3	14	48.1	30.9
	61–90	75.5	6.4	27	39.1	18.3
	91–120	104.6	6.3	17	37.7	17.2
	121–150	132.5	6.6	14	60.6	39.1
	151–180	166.7	6.8	13	75.2	53.1
	181–210	198.3	4.6	10	44.6	29.7
	211–240	220.8	12.8	6	81.5	41.5
	241–270	258.3	8.3	4	46.0	19.0
	271–300	285.7	3.3	7	62.1	51.4
				112		
Demerol 100 mg. plus scopolamine 1/150 grain	1–30	19.4	6.5	15	56.5	33.3
	31–60	46.3	5.2	38	59.6	42.7
	61–90	76.1	6.8	27	58.6	36.4
	91–120	108.6	7.1	16	67.4	40.5
	121–150	129.1	6.3	14	62.0	41.6
	151–180	164.9	8.8	12	92.3	63.5
	181–210	202.7	6.8	6	70.2	47.8
	211–240	228.2	4.6	8	27.1	12.0
	241–270	251.0	13.0	1	163.0	123.0
	271–300	290.3	7.5	4	118.3	93.8
				141		

*The control group was considered to be nonmedicated since the only drug administered to this group was atropine, which "in clinical doses lacks a central sedative effect." From Lull, C. B., and Hingson, R. A.: Control of Pain in Childbirth, Philadelphia, 1945, J. B. Lippincott Company, p. 69.

For convenience of comparison the corrected C-R averages have been plotted against the average Rx intervals for each medicated group in Fig. 2. This

graph has been further simplified by a "rounding of the curve" procedure which is weighted by the number of cases in each group.

The straight line on the graph at the 30.3 seconds level is the corrected C-R average of the control group (35 nonmedicated cases).

Examination of the graph as a whole reveals the striking fact that for all three medications, the longest C-R intervals occur when babies are born about 165 minutes (2 hours and 45 minutes) after maternal medication.

The morphine curve (MS) indicates that the delay in infant respiration was minimal when the baby was born within approximately one hour after morphine administration to the mother. When, however, the child was born from one to three and one-half hours after the mother was given morphine, considerable delay in initial respiration occurred and the maximal C-R interval occurred when the mother was medicated 135 to 195 minutes ante partum.

The effect on the baby of Demerol-scopolamine administration to the mother during labor is indicated by the DS curve of Fig. 2. In this curve the C-R interval of the newborn is relatively uniform for almost two hours at the end of which time it begins to increase. The maximum CR interval occurs at an Rx interval of about 165 minutes.

When the morphine-amphetamine combination was administered the depressing action of the morphine on the newborn was substantially reduced. In comparing the morphine-amphetamine combination (the MA curve) with the control group it may be noted that the average C-R interval on the MA curve remains approximately 10 seconds lower than the nonmedicated control for the first two hours. The subsequent course of the morphine-amphetamine curve peaks at the same Rx interval as with morphine alone but at a level approximately 50 seconds lower.

These data are compared in another way. First, the number of babies breathing in 30 seconds or less were counted in each medication group and control group, ignoring the Rx intervals. Second, the number of babies breathing in 60 seconds or less were counted. This was continued, by half-minute intervals up to 3 minutes. Because of the unequal number of cases in the four groups these data have been expressed as percentages and as such are presented in Table II.

TABLE II. COMPARISON OF INFLUENCE OF MATERNAL MEDICATION ON THE PERCENTAGE OF BABIES BREATHING IN SUCCESSIVE HALF-MINUTE PERIODS

MEDICATION	NUMBER OF CASES	PERCENTAGE OF BABIES BREATHING WITHIN IN SECONDS					
		30	60	90	120	150	180
Nonmedicated	351	66.0	84.5	93.7	96.9	98.0	99.1
Morphine-amphetamine	112	58.9	78.6	91.1	95.5	98.2	99.1
Morphine	38	34.2	65.8	78.9	86.8	92.1	94.7
Demerol-scopolamine	141	49.6	74.5	85.5	92.2	94.3	95.7

Examination of Table II reveals that within the first 2 minutes the largest percentage of cases occurs when no drug has been given to the mother in labor.

It is striking that the percentages of babies shown in each 30-second column for morphine-amphetamine most closely approximate the control percentages, while the percentages in the morphine group uniformly differ the most from the control.

Statistical Analysis

To ascertain the confidence with which the above data may be interpreted and the assurance with which we may draw our conclusions, the data presented in Tables I and II have been submitted to statistical treatment.

The procedure employed to study the significance of the differences between the means is the classical "t" ratio determination. The data from the early

TABLE III. "t" RATIOS* AND PROBABILITIES† OBTAINED WHEN THE DATA OF THE THREE MEDICATED GROUPS AND THE NONMEDICATED GROUP ARE COMPARED, ONLY CASES WHEN MEDICATION PRECEDED BIRTH BY 90 MINUTES OR LESS BEING USED

COMPARISON	"t"	P LIES BETWEEN
Control vs. morphine	0.424	0.6 and 0.5
Control vs. morphine-amphetamine	2.90	0.01 and 0.001
Control vs. Demerol-scopolamine	1.51	0.2 and 0.1
Morphine vs. morphine-amphetamine	1.93	0.05
Morphine vs. Demerol-scopolamine	0.1342	0.9 and 0.8
Morphine-amphetamine vs. Demerol-scopolamine	2.89	0.01 and 0.001

*$"t" = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{n_1 n_2 (n_1 + n_2 + - 2)}{(n_1 + n_2)\ Sx_1^2 + Sx_2^2}}}$

$Sx^2 = \Sigma x^2 - (\Sigma x)^2/n$

†P values from Fisher's Table VA.

When P is 0.05 or less, the differences between means are considered to be significant, but when P is 0.01 or less, a high order of significance exists.

plateaued curves of Fig. 2 (Rx 1 to 90 minutes) are so treated, and the values obtained are presented in Table III.

The probability values in Table III indicate that when babies are born within 90 minutes after their mothers are given morphine-amphetamine, the average C-R interval is significantly shorter than:

1. The control average C-R interval; there being less than one chance in one hundred of coincidence being responsible for the difference.
2. The average C-R interval of babies born within 90 minutes after their mothers had been given Demerol-scopolamine. There is less than one chance in one hundred that this difference is coincidental.
3. The average C-R interval of babies whose mothers had received morphine 90 minutes or less ante partum. There are about five chances in one hundred that this difference is due to coincidence.

Within this Rx interval, there were no significant differences between the control and the Demerol-scopolamine C-R intervals, the control and the morphine C-R intervals, and the morphine and the Demerol-scopolamine C-R intervals.

The "t" ratios and the probability levels for the peak areas of the curves appear in Table IV. The peak area occurs 120 to 210 minutes after the mother was medicated. From these probability levels we learn that:

1. We may be confident that the difference between the peak area of the morphine curve and the control line is real because there is less than one chance in one hundred that coincidence could account for this difference.
2. We may be confident that the difference between the peak area of the Demerol-scopolamine curve and the control line is significant because there is less than one chance in one hundred that this would happen in random sampling by pure chance.
3. There is no significant difference between the peak area of the morphine-amphetamine curve and the control.

Table IV also shows that when morphine is given to the mother 120 to 210 minutes before delivery the first respiration of the infant is delayed significantly longer than when either the morphine-amphetamine combination, or Demerol-scopolamine is given at the same antepartum time. Statistically there is less than one chance in one hundred that the difference between morphine and morphine-amphetamine is coincidental. There are less than five chances in one hundred that the difference between morphine and Demerol-scopolamine is coincidental.

The "Chi Square" procedure has been employed to test the data presented earlier in Table II showing the percentage of infants breathing in successive time intervals. As the time intervals progress, it is obvious that the percentage will ultimately reach 100 per cent in any group; therefore, real advantage exists

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TABLE IV. "t" RATIOS AND PROBABILITIES OBTAINED WHEN THE DATA OF THE THREE MEDICATED GROUPS AND THE NONMEDICATED GROUP ARE COMPARED, ONLY CASES WHEN MEDICATION PRECEDED BIRTH BY 120 TO 210 MINUTES BEING USED

COMPARISON	"t"	P LIES BETWEEN
Control vs. morphine	5.250	0.001 and 0.0001
Control vs. morphine-amphetamine	1.359	0.2 and 0.1
Control vs. Demerol-scopolamine	2.578	0.01 and 0.001
Morphine vs. morphine-amphetamine	2.690	0.01 and 0.001
Morphine vs. Demerol-scopolamine	2.115	0.05 and 0.02
Morphine-amphetamine vs. Demerol-scopolamine	0.820	0.5 and 0.4

TABLE V. CHI SQUARE* AND PROBABILITY VALUES OBTAINED WHEN THE MEDICATION AND CONTROL GROUPS ARE COMPARED ACCORDING TO THE PERCENTAGES OF BABIES BREATHING IN SUCCESSIVE HALF-MINUTE INTERVALS (DATA OF TABLE II)

COMPARISON		CHI SQUARE	P LIES BETWEEN
Control vs. morphine-amphetamine			
	@ 30 sec.	1.74	0.2 and 0.1
	60 sec.	2.13	0.2 and 0.1
	90 sec.	0.71	0.5 and 0.3
	120 sec.	0.2	0.7 and 0.5
Control vs. Demerol-scopolamine			
	@ 30 sec.	11.33	0.001 and 0.0001
	60 sec.	6.9	0.02 and 0.01
	90 sec.	8.02	0.01 and 0.001
	120 sec.	5.10	0.05 and 0.02
	150 sec.	4.58	0.05 and 0.02
Control vs. morphine			
	@ 30 sec.	14.84	0.001 and 0.0001
	60 sec.	20.08	0.001 and 0.0001
	90 sec.	10.48	0.01 and 0.001
	120 sec.	8.70	0.01 and 0.001
	150 sec.	4.74	0.05 and 0.02
Morphine-amphetamine vs. Demerol-scopolamine			
	@ 30 sec.	0.544	0.5 and 0.3
	60 sec.	0.581	0.5 and 0.3
	90 sec.	1.650	0.2 and 0.1
	120 sec.	1.173	0.3 and 0.2
Morphine-amphetamine vs. morphine			
	@ 30 sec.	4.68	0.05 and 0.02
	60 sec.	2.49	0.20 and 0.10
	90 sec.	3.949	0.05 and 0.02
	120 sec.	3.446	0.10 and 0.05

From Snedecor, G. W.: Statistical Methods, Ames, Iowa, 1946, Iowa State College Press, pp. 198-199.

$$*\text{Chi Square} = \frac{(a\,d - b\,c)^2 n}{(a+b)\,(c+d)\,(a+c)\,(b+d)} \qquad n = a+b+c+d$$

when a treated group compares favorably with the untreated group in the early intervals. The statistical information contained in Table V shows us that when babies born of nonmedicated mothers are compared with babies born of medicated mothers:

1. There is a significant difference in the percentage of babies breathing within 2½ minutes in the case of babies delivered of mothers given morphine with the greatest significance of difference occurring within the earliest time periods.

2. There is no significant difference in the percentage of babies breathing in 2½ minutes in the case of babies born of mothers given Demerol and scopolamine with the greatest significance of difference occurring within the first 1½ minutes.

3. There is no significant difference in the percentage of babies breathing even within the first 30 seconds in the case of those babies delivered of mothers given the morphine-amphetamine combination.

Comment

It should be noted that several possible sources of error exist in the data reported. In the first place, we recognize that the interval between the delivery of the chin and the first respiration is not necessarily the best, nor is it the only measure of an infant's respiratory status. As stated earlier, the C-R interval is practical to obtain in large numbers of cases and it can be recorded without the influence of prejudice or personal opinion.

The fact that numerous observers recorded the data is a source of error which we have sought to minimize by discussing and explaining our problem and procedure directly with the anesthesiologists and anesthetists of the participating hospitals.

Major obstetrical variables have been minimized by exclusion of the previously numerated complications from our series. We have further simplified this report by using cases of comparable inhalation analgesia and/or anesthesia. Variables which we cannot minimize or recognize should occur with reasonably uniform frequency in each group, and with sufficiently large numbers of cases in each group these errors should be equalized. Uncontrollable variables increase the heterogeneity of the group and thus increase the magnitude of the differences required for significance to be achieved.

That the influence of cyclopropane anesthesia during labor might influence the neonatal respiratory incentive was anticipated, not only from general opinions expressed on this subject, but particularly from the work of Lund,[19] who found that as cyclopropane duration increased before birth so did the incidence of asphyxiated babies. It was no surprise, therefore, to find that a direct linear relationship existed between the duration of cyclopropane anesthesia and the interval between delivery of chin and first respiration. The correlation coefficient of 0.309 for 199 cases indicates that the possibility of coincidence causing this relationship is very remote indeed.

Although for the sake of convenience we have used the correction factor of 3.26 seconds for each minute of cyclopropane anesthesia over the entire anesthesia time range (1-18 minutes), we realize that the true linearity probably does not hold for the first four minutes of anesthesia, and that during this time the respiration increment is probably at a lower rate than 3.26 sec. per minute. This observation is also consistent with Lund's statement:

"With it [cyclopropane] neonatal asphyxia was at its minimum when administration was limited to 5 minutes; in fact, at this time interval it surpassed the other agents under consideration. Asphyxia increased rapidly as the time of administration increased. . . ."

A far more detailed and critical study of the influence of "analgesic-anesthetic" gases on the C-R interval is certainly indicated. Before discussing the comparative effects of the different analgesic drugs on the C-R interval an explanation of our interpretation of this interval will be given. We believe that the duration of this interval is determined by the activity of the complex mechanism which culminates in initial respiration. The duration is inversely related to the "respiratory incentive."

The C-R interval is obviously related to the status of the respiratory center. It can be influenced directly by narcotics and excitants, but other factors such as the duration of exposure to hypoxia and hypercapnia also may play important roles.

Fig. 2 shows that there is little depression of respiratory incentive if the baby is born sooner than 60 to 75 minutes or longer than 270 minutes after his mother is given ⅙ grain of morphine. However, between Rx intervals of 75

and 165 minutes the depressing action of morphine increases until maximal depression is reached at 165 minutes. Depression of the respiratory incentive of the infant then begins to diminish until the depression is about spent at approximately 285 minutes.

These findings correspond with those of Shute and Davis[20] who noted the incidence of narcotized babies born of mothers who had been given ¼ or ⅙ grain of morphine. They found minimal incidence of narcotized babies when birth occurred 3½ hours (210 minutes) after maternal medication.

A common statement in the literature on obstetrical analgesics is that morphine is the most reliable and satisfactory analgesic available except for its hazard to the respiration of the newborn. Our experience with morphine is another confirmation of this hazard.

As stated earlier, we have included a series of cases with Demerol-scopolamine medication because of its popularity among obstetricians. Demerol and scopolamine were found to delay significantly the infants' respiration, indicating that Demerol-scopolamine is a relative hazard to the infant but not as great as morphine.

Since babies born within 90 minutes after the mothers are medicated with the morphine-amphetamine combination not only breathe significantly sooner than babies of morphine- or Demerol-scopolamine-treated mothers, but also significantly sooner than babies born in the control series, and since during the maximal depression period (120-210 minutes) the babies in the morphine and Demerol-scopolamine series breathe significantly later than those in the control group, while the morphine-amphetamine babies do not, we conclude that when amphetamine is used to supplement morphine there is less hazard to the newborn than when the mother is medicated with either morphine or Demerol-scopolamine. In addition, it is our clinical impression that this combination improves maternal analgesia and may produce euphoria in the mother which leads us to believe that morphine-amphetamine is worthy of broader clinical trial when obstetrical analgesia is desired.

Summary and Conclusions

1. The interval between the delivery of the chin and the first respiration of the newborn has been used as a criterion for studying the influence of analgesic drugs in obstetrics.

2. Cases were selected in which the mothers had been given (a) no analgesic drug, 350 cases, (b) ⅙ grain of morphine, 38 cases, (c) ⅙ grain of morphine followed by 5 mg. of d-amphetamine or 10 mg. of dl-amphetamine, 112 cases, and (d) 100 mg. of Demerol plus 1/150 grain of scopolamine, 141 cases. Further selection was made on the basis of inhalation analgesia and/or anesthesia employed ante partum. All types of obstetrical abnormalities were excluded.

3. We have attempted to validate objectively our clinical impression that antepartum amphetamine is of real benefit to the newborn.

4. In the nonmedicated group it was found that each minute of cyclopropane anesthesia delayed the chin-respiration interval 3.26 seconds. From this a correction factor was established to eliminate the influence of the anesthesia.

5. After the anesthesia correction factor was applied the nonmedicated group (350 cases) was found to have a chin-respiration average of 31.9 seconds. This control average was used as a basis for comparison of the influence of the drugs.

6. Both morphine and Demerol-scopolamine were found to delay respiration of the newborn significantly when statistically compared with respiration of infants in the nonmedicated control group.

7. Morphine followed by amphetamine, when compared with results in the control group, was found to produce no significant delay in the initial respiration.

8. The introduction of amphetamine into obstetrical analgesia provides a way of using time-honored morphine for relief of pain in labor with minimal hazard to the newborn.

References

1. Lull, C. B., and Hingson, R. A.: Control of Pain in Childbirth, ed. 2, Philadelphia, 1945. J. B. Lippincott Company.
2. Schmidt, R.: Med. Klin. 37: 1485, 1912.
3. Gaisboeck, F.: Med. Klin. 9: 405, 1913.
4. Muir, E.: Proc. Roy. Soc. Med. 20: 997, 1927.
5. Cochrane, R. G.: Lancet 217: 551, 1929.
6. Buscaino, V. M., and Pero, C.: Rassegna internaz. di clin. e terap. 21: 691, 1940.
7. Goetzl, F. R., Burrill, D. Y., and Ivy, A. C.: Proc. Soc. Exper. Biol. & Med. 55: 248, 1944.
8. Ivy, A. C., Goetzl, F. R., and Burrill, D. Y.: War Med. 6: 67, 1944.
9. Burrill, D. Y., Goetzl, F. R., and Ivy, A. C.: J. Dent. Res. 23: 337, 1944.
10. Ivy, A. C., Goetz, F. R., Harris, S. C., and Burrill, D. Y.: Quart. Bull. Northwestern University M. School 18: 298, 1944.
11. Abel, S., and Harris, S. C.: Federation Proc. 6: p. 67, 1947.
12. Harris, S. C., and Friend, F. J.: Federation Proc. 6: p. 124, 1947.
13. Friend, F. J., and Harris, S. C.: J. Pharmacol. & Exper. Therap. 93: 161, 1948.
14. Handley, C. A., and Ensberg, D. L.: Anesthesiology 6: 561, 1945.
15. Prinzmetal, M., and Alles, G.: Proc. Soc. Exper. Biol. & Med. 42: 206, 1939.
16. Schulte, J. W., et al.: J. Pharmacol. & Exper. Therap. 71: 62, 1941.
17. Prinzmetal, M., and Bloomberg, W.: J. A. M. A. 105: 2051, 1935.
18. Friedman, H. A., and Harris, S. C.: Am. J. M. Sc. In press.
19. Lund, C. J.: Am. J. Obst. & Gynec. 43: 365, 1942.
20. Shute, E., and Davis, M. E.: Surg., Gynec. & Obst. 57: 727, 1933.
21. Cole, W. C., Kimball, D. C., and Daniels, L. E.: J. A. M. A. 113: 2038, 1939.
22. Snyder, F. F.: Obstetric Analgesia and Anesthesia, Philadelphia, 1949, W. B. Saunders Company, pp. 166-185.

Discussion

DR. MARY KARP.—I have found Dr. Abel's well-presented paper both interesting and instructive. Such a comprehensive clinical study can be lauded with enthusiasm. The statistics are checked and rechecked so that final conclusions and remarks seem most accurately deduced. Though amphetamine may have a potentiating effect on morphine analgesia it also has waking effects on sedatives and hypnotics. A balance must be reached whereby maximum analgesia may result with minimum antagonism to the hypnotic and narcotic sedative drugs. In a study of this kind I wonder whether one can so fully eliminate the influence of the anesthesia administered? The source of error has been reduced in this statistics study to a minimum. However, one has the feeling that the course of the anesthesia period could certainly influence the C-R interval, regardless of the time of anesthesia and the agent used. The amount of the drug needed in a specific case, the possibility of cyanosis, laryngospasm, salivation—all these may affect the infant. Also the plane of anesthesia would appear to me to be an important factor. It has appeared to us as anesthetists that patients receiving amphetamine are more alert, and take more anesthesia during the second stage of labor. This may be due to the effect of the amphetamine in addition to the increased metabolic requirements of the parturient. It would be interesting to do a study in which amphetamine alone is used plus local or regional blocks. Perhaps this would give adequate analgesia with a reduction of the period of C-R interval, and one is led to believe this from the last chart shown by Dr. Abel.

Or, perhaps the addition of amphetamine with methadon to aggravate the analgesic effect might be worth studying.

How much antagonism or synergysm is there between morphine and amphetamine? Should morphine be entirely eliminated? This would suggest a series run with amphetamine only for its influence on the infant.

Digressing somewhat from the main contents of the paper I wish to interject a caution in the use of these sympathomimetic drugs during the pregnancy term. It is my feeling that we are getting a hopped-up race of women, and I think that probably 4 out of 10 are taking dextro amphetamine or d-desoxyephedrine in one form or another for the euphoria and sense of well-being, or for diet purposes. Though habituation is not seen, too often cases have come to my attention of people depending on the drug. It would seem to me possible to overstep with its use on the reserves of a person. This has no significance in the normal patient, but certainly would for the hypertensive patient or a patient with cardiopathy, advanced age, thyrotoxicosis, or the hyperexcited person or those sensitive to ephedrine or related substances.

Again on a tangent, I have used a sister drug, d-desoxyephedrine, in many thousands of cases during and following anesthesia management of our surgical cases, and have found it of value in the following conditions: As a vasopressor during spinal anesthesia, to decrease nausea and vomiting after fenestration surgery, and to provide waking effects against the barbiturates and opiates or other depressant drugs.

I should like to ask Dr. Abel if he has noted any cases of hypersensitivity and excitability to amphetamine.

Again, I am most impressed with such a detailed clinical study and feel that only by such accurate evaluation as this will we come close to the truth about drugs.

DR. E. S. BURGE.—Dr. Abel and his co-workers have added another ingredient to the recipe for the obstetrical philosopher's stone; amphetamine allows us to have some cake and eat a little of it too. Their original experiments with puppies taken from mothers given morphine and amphetamine were so striking that I was anxious to study the effect of Benzedrine in our department at the Evanston Hospital. In collaboration with our Department of Anesthesia, we collected data on the first 250 cases in which Benzedrine was used. We have continued to use it freely, since throughout the study we were impressed with the ability of Benzedrine to lessen the depressing effects of intrapartum medication on the newborn. Our failure to observe definite analgesic action of the Benzedrine was perhaps due to our custom of using scopolamine with whatever analgesic is employed. We were particularly pleased with the amphetamine effect in difficult deliveries. By agreement with the authors we sought the minimum effective time before delivery, or "How late in labor can one give Benzedrine?" Unless the drug is administered at least 40 minutes before delivery, one cannot predict a beneficial effect on the baby. We are now less hesitant to medicate a multipara who may deliver sooner than expected—namely, at the peak of depressant action. As Dr. Abel has said, if delivery takes place within the first 75 minutes of medication, depression of the infant is unusual. If birth takes place in less than the four hours we allow for the usual drugs to lose their greatest effect, Benzedrine gives the infant real protection.

As a discussant, what flaws can I find in this fine work—none of great significance. We used the time from delivery of the chin to the first actual cry as the C-R interval. It seemed a better index of the newborn's vitality, since crying time may be delayed considerably after respirations begin. These early respirations may be grossly inadequate prior to the first cry.

Dr. Abel mentions that the curve showing the influence of cyclopropane on respiratory incentive should be flat during the first 4 or 5 minutes. I am surprised, and pleased for Dr. Abel's babies, that the longest C-R interval under any duration of cyclopropane was 105 seconds. I am sure the chin-to-crying time was much longer in many cases. I should like, parenthetically, to insert a clinician's complaint on cyclopropane. Despite the learned arguments of the anesthesiologists, to me, the depressant effect of cyclopropane on the newborn exceeds that of ethylene, ether, or nitrous oxide. If time allows, I would appreciate Dr. Abel's comment on this point.

We have used a good deal of "saddle block" anesthesia at Evanston in the past 4 years. Early in our Benzedrine study we found it most important *not* to use ephedrine to

support the blood pressure after spinal injection. The combined effect of Benzedrine and ephedrine can give immediate and alarming hypertension with excruciating headache.

Three babies were definitely flushed and hypertonic in the early cases, but we were then drawing the 10 mg. dose from the only available ampule containing 20 mg. of Benzedrine in solution. We thought overdosage the probable answer.

One obstetrician at Evanston no longer uses Benzedrine because he feels his patients do not get to sleep after returning to their rooms. I have no data on the B-S, or birth to sleep, interval but am inclined to believe it often prolonged.

DR. S. C. HARRIS.—Some points came up which I would like to have Dr. Abel answer since they are clinical. There are a few things I would like to clarify. There is a widespread opinion that Dexedrine stimulates metabolism much as thyroid does. I do not believe that this is true. We have studied a very large group of normal human subjects on 30 mg. per day and a constant caloric intake. These subjects lost no weight. I think this is good evidence that Dexedrine does not influence metabolism.

In the matter of employing drugs such as morphine, there have been many tests of the drug by ourselves and others and we are in substantial agreement that it is analgesic. We have reported many times that we get a better analgesic effect from morphine by adding Benzedrine. We have used Benzedrine and others have used Dexedrine. I might say that the most effective analgesic I have ever seen is epinephrine. We have on a number of occasions done complete laparotomies on conscious dogs with no anesthetic, treating the dogs with nothing other than 0.5 c.c. of epinephrine hydrochloride in the carotid artery before this operative procedure. The animals were entirely unconcerned about the operation. As we talked to the dogs they wagged their tails.

The mechanism is probably more involved than we have time to or are able to discuss. I might add one more point about the role of the adrenal substance, epinephrine, in analgesia. We as well as others have eliminated the analgesic effects of morphine with some anesthetic agent by adrenalectomy. The adrenal medullas were removed and these animals were no longer rendered insensitive when morphine was given postoperatively.

The comment Dr. Burge made about the correlation between the C-R interval in babies and the anesthesia is pertinent. We should recognize that the curve in the graph showing the influence of cyclopropane on respiratory incentive should be flat in the first four or five minutes. In our study 3.6 minutes was the point we have assigned for cyclopropane anesthesia. We are, however, doing a more meticulous study of the influence of different anesthetic agents on this C-R interval. There are many factors involved. We believe that a lot of these factors cancel out as the number of cases in each group increases. If the records were not kept well for us we would have nothing to report at this time. The other things that we will report on are other drugs, medications, etc. It has taken us years to examine the protocols of every case that graces our tabulations. We have learned the same things over and over. I hope at some future time we will be able to present more of our findings.

DR. ABEL (Closing).—In answer to Dr. Karp, we do have on occasion excitable patients. I mentioned a little earlier that we are now studying the time of administration of some of these drugs. We have held off with Benzedrine until we have had the full effect of morphine, and then a little later in the delivery began the Benzedrine. This has proved satisfactory.

I think Dr. Burge is quite correct about the cry interval. Sometimes babies take a preliminary breath and then do not cry. We are not absolutely satisfied with this C-R interval. Dr. Burge asks if 105 seconds C-R interval is the poorest interval in our series. My babies are all not quite that responsive. These are the *averages* of all cases along the line, after correction for the anesthetic factor.

With regard to cyclopropane, I feel it is a depressant. A short time ago we considered the propriety of using cyclopropane instead of ethylene. I thought the increased oxygenation in such cases would perhaps offset the disadvantages of cyclopropane. I do not think it has. I think there is still a depression of the respiratory center. The B-S interval (birth-sleep) is increased. However, we have felt that we are at liberty to give whatever is needed for sleep.

EPITHELIAL CHANGES IN THE PUERPERAL FALLOPIAN TUBE

MASON C. ANDREWS, M.D.,* BALTIMORE, MD.

(From the Department of Obstetrics, Johns Hopkins University and Hospital)

THE cyclical changes of the epithelium of the human Fallopian tube during the menstrual cycle have been described in detail by Novak and Everett[1] and by Snyder.[2] Its morphology during pregnancy prior to delivery has been mentioned by them.[1, 2] The purpose of the present communication is to describe the changes which occur during pregnancy and the puerperium and to report the effect on this epithelium of the administration of estrogen and progesterone singly and in combination.

A brief review of the morphology of the tubal epithelium and its changes in nonpregnant women seems desirable for orientation. This is based principally on the work of Novak and Everett[1] and is illustrated in textbooks.[3] There are three principal types of cells: (1) ciliated, (2) nonciliated, (3) peg cells.

Ciliated Cells.—These cells are characterized by rather long, plainly visible cilia, ovoid pale-staining nuclei often at right angles to the axis of the cell, and pale-staining cytoplasm. Variation in height and width under hormonal influences causes a change from cuboidal to tall columnar shape. The nuclei tend to be situated nearer the ciliated luminal margin of the cell.

Nonciliated Cells.—These also vary in size with hormonal changes but to a lesser degree. In general they are narrower and contain less cytoplasm which stains darker. The nuclei are elongated, oval shaped, deeply staining and in the long axis of the cell.

Peg Cells.—These are probably merely one stage in the cyclic alterations of the nonciliated cells resulting from extrusion of cytoplasm. They seem to consist only of a compressed nucleus similar to that of a nonciliated cell but on close observation have a very small amount of cytoplasm.

There are, in addition, scattered along the course of the epithelium "wandering cells" occurring in much smaller numbers than the above-mentioned cells but consistently found at all times. These small, usually round cells are wedged between the epithelium and the submucosa. Although Sampson[4] suggested they were characteristic of the Müllerian mucosa, they are probably wandering cells.[1, 4] The cytoplasm does not stain at all and the nucleus is round, small, and stains heavily.

Cyclical Changes.—In the early postmenstrual phase the epithelial cells are rather uniformly low (10 to 15 microns at the end of menstruation), containing less cytoplasm and being closely packed. The nonciliated cells are quite narrow. By the end of the fourth day following menstruation there has been a great and uniform increase in the height of both types of cells. The late proliferative phase presents a characteristic picture in which the epithelium is quite tall and regular (Fig. 1). There is great increase in the cytoplasm of both types of cells with their nuclei appearing to form two layers, those of the ciliated cells tending to be situated nearer the lumen. The figure of 25 or even 30 microns is mentioned[1] as the height attained by the epithelium. Our

*Present address, Medical Arts Building, Norfolk, Va.

measurements in only eight cases during the late proliferative phase indicated a range from 18 to 25 microns with an average height of 21 microns. The luminal margin of the epithelium consists principally of ciliated cells separated by narrow cytoplasmic projections from the nonciliated cells. Near ovulation maximum height is reached. The cytoplasm of the ciliated cells becomes quite light with perinuclear vacuoles resembling those seen in the glandular epithelium of the endometrium at the same stage. The nuclei of the

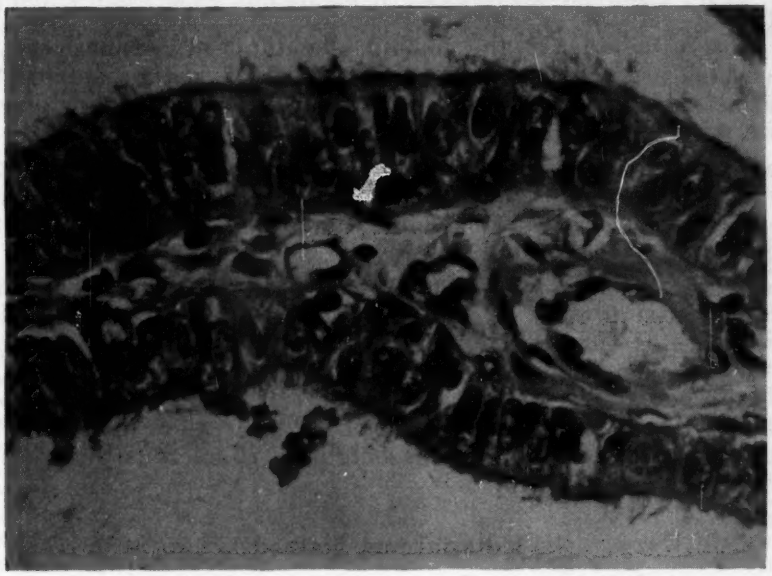

Fig. 1.—Late proliferative phase. Both ciliated and nonciliated cells are uniformly tall. The cytoplasm of the ciliated cells is much increased and perinuclear vacuoles are abundant. (×600.)

Fig. 2.—Tubal epithelium from case showing endometrial hyperplasia. There is further increase of estrogenic changes with great predominance of the ciliated cells. (×600.)

ciliated cells are larger and paler staining than at other times in the cycle. In the early secretory phase, beginning gradually several days beyond ovulation, a process of recession begins which continues to the end of menstruation. The size of the ciliated cells decreases particularly in the longitudinal dimension making the edge irregular as the cytoplasm and nuclei of the nonciliated cells tend to move toward the surface in increasing numbers and to be extruded into the lumen either as cytoplasm or isolated nuclei. This process becomes much more marked during the premenstrual phase and the height of both types of cells is considerably diminished. The nonciliated cells are crowded closely together as the amount of cytoplasm becomes less, and some peg cells which are now seen in quantity for the first time apparently result. During menstruation the same process continues diminished and the epithelium reaches its minimum height and stage of apparent inactivity.

In postmenopausal women the epithelium uniformly decreases gradually in height with loss of rugae. Some cilia usually persist. The two cases encountered in this study showed obvious cilia 10 and 20 years postmenopausally and measured 10 and 8.8 microns in height.

Endometrial Hyperplasia.—Tubes removed with uteri which show endometrial hyperplasia present an exaggeration of the changes found during the estrogenic phase of the menstrual cycle (Fig. 2). The height of both types of cells is further increased, but the border is regular. The ciliated cells are remarkably predominant in number and size. The cytoplasm becomes even less dense, particularly about the nucleus. Measurement in the single case in the present study showed an average height of 28 microns though heights up to 35 microns are mentioned.[1]

Material and Methods

The material used for the present study is derived principally from the sections of Fallopian tubes obtained at puerperal sterilizations done at the Johns Hopkins Hospital between 1941 and 1947. These portions were usually from the middle third of the tube. Eighty-four cases were selected to provide a representative distribution among the various days of the puerperium and during pregnancy as shown in Table I. Where the entire group from any one day was not used, the selection was random. Sections from 28 nonparturient patients in whom the tubes were removed as part of a gynecological operation were studied with endometrium when available.

The height of the epithelium (exclusive of cilia) was measured by means of a calibrated eye piece with the average measurements of 10 representative areas of each section used.

During the course of the study an additional six cases treated preoperatively with hormones were added. Stilbestrol, 5 mg. daily and progesterone were given simultaneously to 4 patients beginning on the day of delivery and extending to the time of operation from five to nine days post partum. Three received 100 mg. progesterone intramuscularly in divided doses each day; the fourth had 25 mg. daily. Two patients were given 5 mg. stilbestrol for ten and five days prior to hysterotomy (24 weeks) and cesarean section, respectively. One patient was given progesterone alone (100 mg. daily) from delivery to operation on the sixth day.

Results

Two distinct trends were found in the epithelium with increasing days post partum. By the fifth postpartum day, one group showed a proliferative change closely resembling that seen in association with endometrial hyper-

plasia, while the other group showed a definite diminution in the size and apparent activity of the cell epithelium resembling its appearance in senility.

It was suspected that the typically estrogenic proliferative changes might have resulted from the puerperal administration of estrogen. A review of the clinical histories of all patients showed that those with proliferative changes had uniformly received stilbestrol (Fig. 3). This had been given routinely to all postpartum patients in 1942 to study its effect on puerperal morbidity[5] and has frequently been used subsequently to suppress lactation. The dose in almost every case was 5 mg. daily from the day of delivery. Only one case of the 15 which had been treated with stilbestrol failed to show obvious and measurable proliferative changes. This patient, operated upon 72 hours post partum, may have failed to take her medication.

TABLE I. SOURCES OF FALLOPIAN TUBES STUDIED IN 112 CASES, AND AVERAGE HEIGHT OF EPITHELIUM

	NUMBER OF CASES	AVERAGE HEIGHT UNMEDICATED CASES (MICRONS)	AVERAGE HEIGHT STILBESTROL-TREATED CASES (MICRONS)
Sterilization of Parturients.—			
At hysterotomy	5	16.0	
At cesarean section	10	14.0	
Postpartum day 1	4	17.0	
Postpartum day 2	8	12.6	
Postpartum day 3	7	14.1	23.0
Postpartum day 4	8	12.3	15.7
Postpartum day 5	6	10.6	25.9
Postpartum day 6	7	11.3	20.3
Postpartum day 7	7	11.6	20.4
Postpartum day 8	6	10.4	
Postpartum day 9	5	10.2	25.3
Postpartum day 10	5	9.8	25.9
Postpartum days 11-14	6	10.0	25.2
Gynecological Operations.—			
During menstrual cycle	25		
Senile	2	9.4	
Endometrial hyperplasia	1	28.0	
Total	112		

Normal Puerperal Changes.—In the unmedicated cases, a consistent diminution in the height and apparent activity of the epithelium is observed. The extrusion of nuclei and cytoplasm from the nonciliated cells continues with decreasing frequency through about the seventh postpartum day and a moderate amount of cellular debris accumulates in the lumen. The nonciliated cells become more compact with less cytoplasm. Simultaneously, the ciliated cells decrease in size and number and the number and size of the cilia of the remaining cells decreases. By the fourteenth postpartum day (Fig. 8) the epithelium is quite similar to that seen in late postmenopausal women, measuring a comparable 10 microns or less. No cilia at all were found in the few sections examined. The ciliated type of cell occurred with much less frequency than in the earlier postpartum days.

Changes Following Estrogen Administration in the Puerperium.—Patients who had received estrogen daily prior to the tubal ligation showed the increase in height and cellular content characteristic of the proliferative phase of the menstrual cycle. The ciliated cells are particularly increased in size, although the height of the nonciliated cells is maintained equally, forming very slender cells. The relative number of ciliated forms is greater. The cytoplasm of both

types becomes paler. This is particularly marked in the ciliated cells where perinuclear clear zones resemble the secretory vacuoles of the endometrium. The nuclei of the ciliated cells become larger and paler, migrating toward the luminal edge.

Within 48 hours after estrogen administration, the characteristic changes are observably and measurably present. By the fifth day the growth corresponds to that at mid-point of the menstrual cycle and before the ninth resembles that found with endometrial hyperplasia (Fig. 6). Mitoses are almost never seen.

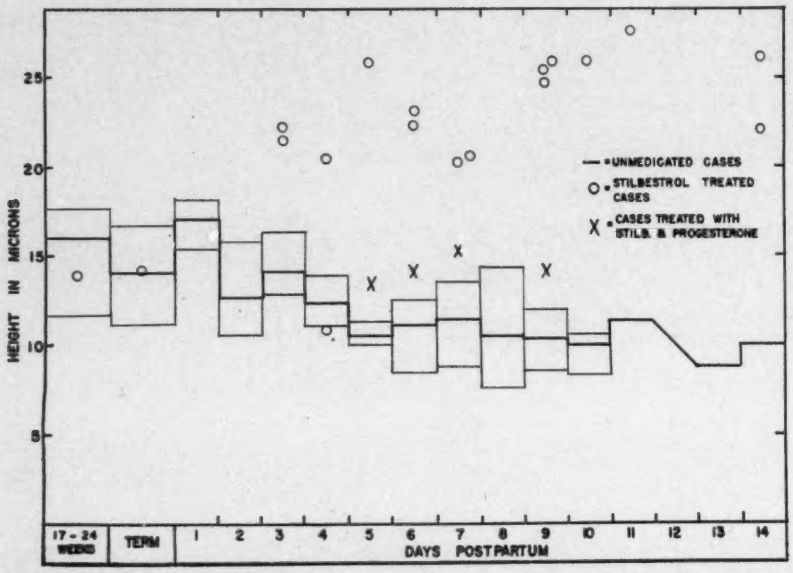

Fig. 3.—Height of tubal epithelium in 90 cases during pregnancy and the puerperium. The heavy lines indicate average height in unmedicated cases and the thin lines show range of values. The number of cases in each group is shown in Table I. Values from medicated cases are so indicated and shown individually.

Effect of Simultaneous Administration of Estrogen and Progesterone in Puerperium.—The four patients given progesterone simultaneously with stilbestrol during the puerperium showed inhibition of the estrogen effect. The heights were equivalent to those found during pregnancy where both hormones were also present (Fig. 7).

Effect of Antepartum Estrogen Administration.—After stilbestrol had been given for ten and five days prior to hysterotomy and cesarean section, respectively, the tubal epithelium showed no deviation from the usual pattern found at these times.

Effect of Progesterone Alone in Puerperium.—The patient given progesterone during the puerperium showed no change from the usual epithelial pattern seen in equivalent unmedicated cases.

Salpingitis.—Thorough examination of all the sections from the sixth postpartum day to the fourteenth showed a gross incidence of inflammatory reactions, in one or both tubes, of 44 per cent. The reaction varied from extensive acute purulent salpingitis to a sprinkling of polymorphonuclear leucocytes in the slightly edematous stroma of the endosalpinx. In about half of the cases the reaction was so mild that a diagnosis of salpingitis would not be made by usual standards. In Table II an attempt is made to divide the cases on this basis. Some cases in which the number of leucocytes seemed too small were

excluded as were cases where concentrations of them were inside the blood vessels or in the lumen of the tube only. The majority of the cases classified here as salpingitis, though definite, were not severe reactions.

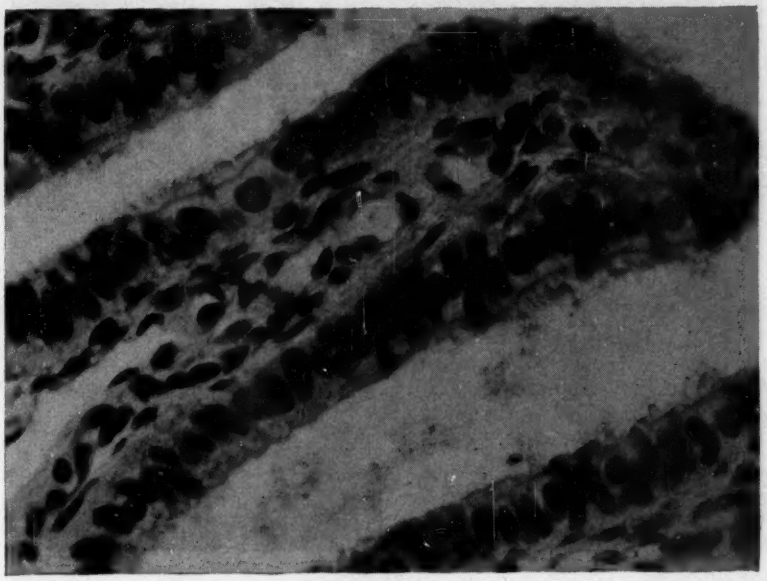

Fig. 4.—Tubal epithelium at the time of cesarean section. All cells are moderately low. There is some extrusion of nuclei. (×600.)

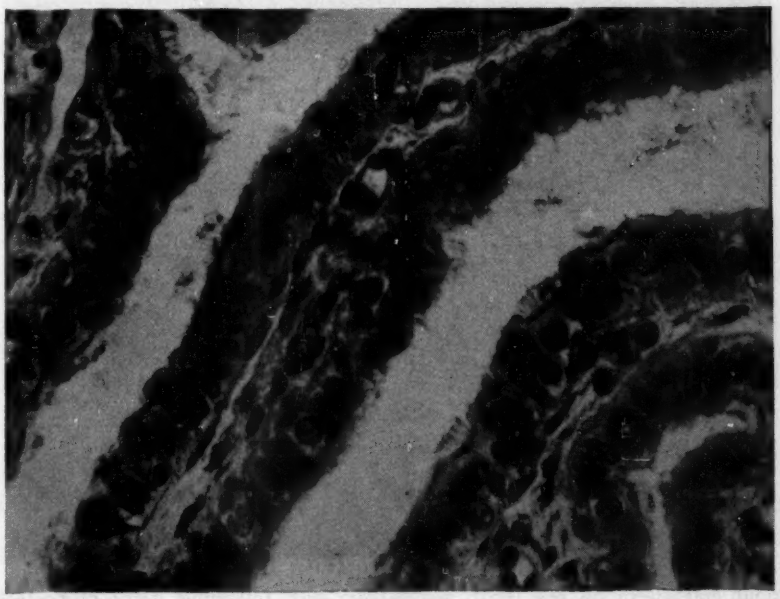

Fig. 5.—Tubal epithelium on the ninth postpartum day in an unmedicated case. Cells are decreased in height and activity with particular recession of ciliated cells. (×600.)

Much cellular debris was often seen in the lumina of tubes with and without inflammatory reaction. The extent and incidence increased with the number of days post partum, being seen mostly after day four, and with the co-

existence of inflammatory reaction. Little or no debris was seen in the lumina of the stilbestrol-treated cases. Inflammatory reactions from the tenth day and beyond tended to contain principally mononuclear leucocytes.

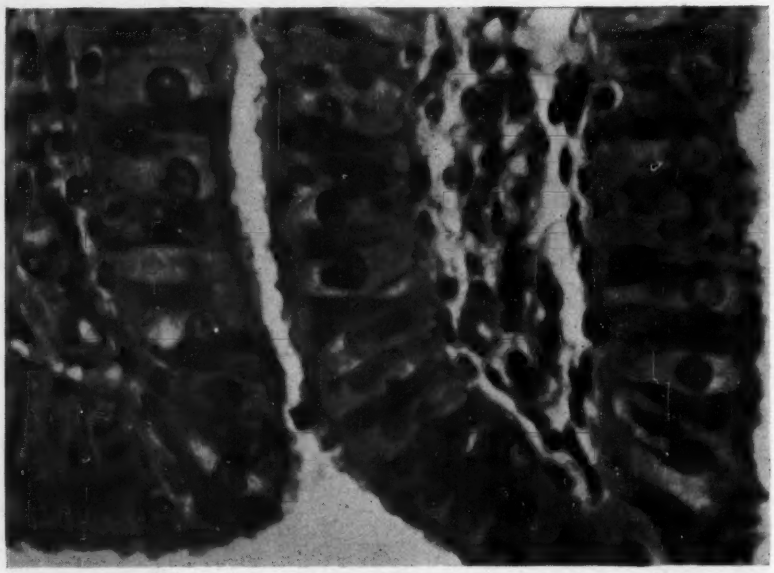

Fig. 6.—Tubal epithelium on the ninth postpartum day following daily stilbestrol. Marked hyperplasia especially involving the ciliated cells. (×600.)

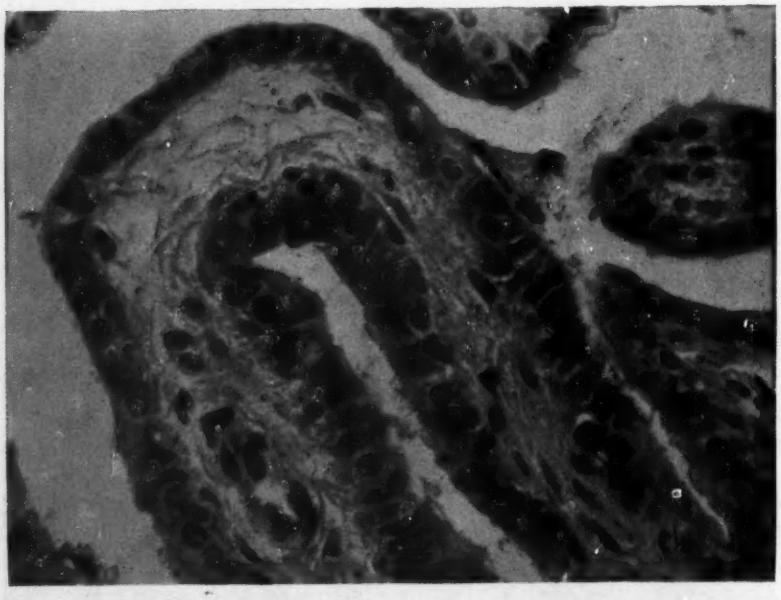

Fig. 7.—Tubal epithelium on the ninth postpartum day following daily stilbestrol and progesterone. Estrogen effect is completely inhibited. (×600.)

Of the 36 cases studied, 12 had received stilbestrol. In none of these 12 cases was a single polymorphonuclear leucocyte found (Table II). In the remaining cases, none of which had received stilbestrol, the incidence of some inflammatory reaction was 67 per cent, and 38 per cent showed salpingitis.

TABLE II. INCIDENCE OF SALPINGITIS IN 36 CASES OF PUERPERAL STERILIZATION BETWEEN FIFTH AND FIFTEENTH POSTPARTUM DAYS

	STILBESTROL MEDICATED			UNMEDICATED CASES		
DAY POST PARTUM	NUMBER CASES	SALPINGITIS	MINIMAL INFLAMMATORY REACTION	NUMBER CASES	SALPINGITIS	MINIMAL INFLAMMATORY REACTION
6	3	0	0	4	0	2
7	2	0	0	5	2	1
8	0	0	0	6	3	3
9	3	0	0	2	1	0
10	1	0	0	4	1	1
11	1	0	0	1	1	0
12	0	0	0	0	0	0
13	0	0	0	1	1	0
14	2	0	0	1	0	0
Total	12	0	0	24	9	7

Of four patients treated with stilbestrol and progesterone, one showed marked salpingitis and a second showed inflammatory reaction. The former had received penicillin, 600,000 units each day for three days preoperatively, and the latter 600,000 units for one day preoperatively.

Bacterial stains on all 16 sections listed as showing inflammatory changes failed to demonstrate bacteria in any. They were prepared and examined by experienced pathologists.

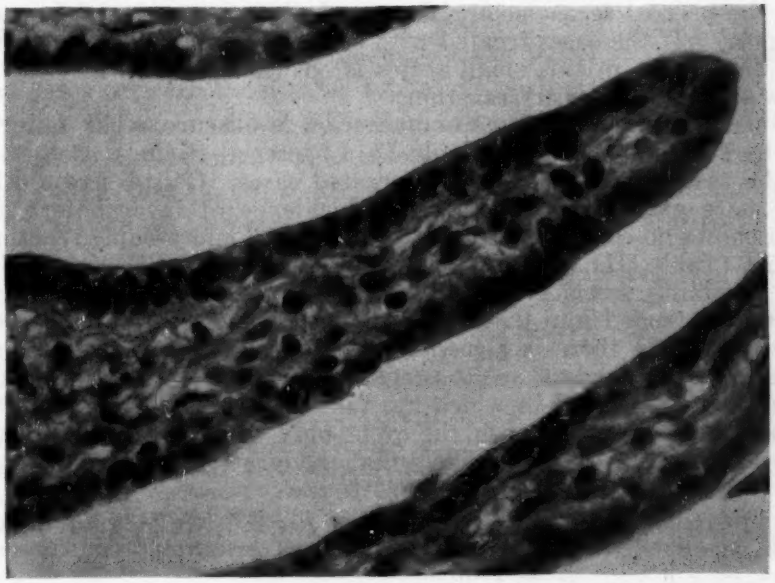

Fig. 8.—Tubal epithelium on the fourteenth postpartum day. Marked atrophy and inactivity with loss of cilia resembling senility. (×600.)

Comment

As clearly demonstrated by Novak and Everett in 1928, the epithelium of the Fallopian tube responds characteristically to the hormone variations during the menstrual cycle. The other changes described above are all predictable on the basis of present knowledge of the secretion of estrogen and progesterone.

During the first half of the menstrual cycle, the increase in height and other characteristic changes affecting principally the ciliated cells are the

result of stimulation by estrogen. There is an exaggeration of this effect in cases with associated endometrial hyperplasia, presumably due to hyperestrinism.

During the second half of the menstrual cycle, under the influence of progesterone, and in the presence of some estrogen, the height diminishes, the ciliated cells regress markedly, and the nonciliated cells show marked activity in the extrusion of nuclei and cytoplasm. During menstruation, when the hormone levels are minimal, the height and apparent activity of the cells are lowest.

If pregnancy results, the progestational changes continue and the epithelium remains low with moderate evidence of extrusion of nuclei of nonciliated cells and a predominance of these cells. This situation is maintained throughout pregnancy. After delivery and withdrawal of estrogen and progesterone, there is a slight flurry of some increase of extrusion and a further diminution in the height and activity of both types of cells.

The epithelium shows marked response to estrogen administered in the puerperium or secreted in the first half of the menstrual cycle and yet fails to respond to the much greater quantities present during pregnancy. This must be the result of inhibition by the progesterone present concomitantly in the latter case. To demonstrate this, stilbestrol and progesterone were administered simultaneously to four patients and the estrogenic effect was inhibited (Fig. 7). Similarly, the estrogen administered ante partum produced no effect as expected because of the presence of progesterone.

A 27 per cent incidence of salpingitis in the puerperal Fallopian tube beyond the fifth day post partum has been reported by Hellman.[6] The incidence in the present series, comprising much the same material, is comparable (25 per cent). If the cases treated with stilbestrol are excluded, the incidence of acute salpingitis in this small series is 38 per cent, and a total of 67 per cent show some inflammatory reaction.

The basis for this inflammatory reaction is obscure. The failure to find bacteria by staining casts some doubt on a bacterial etiology as does the presence of the reaction in two penicillin-treated cases. Cultures would be necessary for more exact information. The incidence of fever before and after operation shows no consistent correlation with the microscopic reaction in this small series (Table III).

The possibility seems greater that the reaction is the response to cellular debris, either extruded into the lumen or refluxed from the uterus as suggested by Everett.[7] While there is a moderate cellular extrusion in the early puerperium, there is much more in the progestational phase of the menstrual cycle. Of the ten cases examined in which the tubes were obtained between the nineteenth and twenty-eighth days of the cycle, only two showed a minimal inflammatory reaction. It seems more likely that the large quantity of cellular debris

TABLE III.—INCIDENCE OF FEBRILE REACTION* IN 36 CASES IN WHICH TUBAL LIGATION WAS PERFORMED BETWEEN THE FIFTH AND FIFTEENTH POSTPARTUM DAYS ACCORDING TO PATHOLOGICAL FINDINGS

		BEFORE OPERATION		AFTER OPERATION	
	NO. CASES	FEVER 1 DAY	FEVER 2 DAYS	FEVER 1 DAY	FEVER 2 DAYS
Unmedicated.—					
Salpingitis	9	4	2	7	4
Mild inflammatory reaction	7	1	0	3	1
No inflammatory reaction	8	3	2	4	3
Stilbestrol-Treated Cases.—					
No inflammatory reaction	12	0†	3	0†	2

*Temperature 100.4° F., excluding the first 24 hours post partum.

†Figures not obtained.

seen in the lumina of many puerperal tubes is reflux from the uterus. One would expect some bacteria in such material, increasing with the number of days post partum. The factors responsible for the influx of leucocytes into the premenstrual endometrium apparently do not produce a comparable change in the endosalpinx at that time and there seems no real reason to suppose they are responsible for the postpartum inflammatory reaction in the tube.

The complete absence of the inflammatory reaction in the stilbestrol-medicated cases could well be the result of the more efficient clearing of the tube by the heavily ciliated epithelium plus some protection afforded by the double thickness attained by these cells. Some similar protection of the endosalpinx may be present during the proliferative and early secretory phases of the menstrual cycle and may contribute to the tendency of salpingitis to occur initially or flare up near the time of menstruation.

Hellman[8] has suggested that "one child sterility" may result from a salpingitis which is merely an extension of the inflammatory reaction commonly found in the puerperium.

Summary

1. The epithelium of the human Fallopian tube becomes progressively lower and more inactive following delivery, and by the twelfth day resembles that found after menopause.

2. Stilbestrol administration to puerperal women produces rapid and marked hyperplasia of the tubal epithelium.

3. Progesterone administered simultaneously with stilbestrol prevents the hyperplastic change.

4. Acute salpingitis, mild to moderate, was found in 38 per cent of unmedicated cases between the fifth and fifteenth postpartum days.

5. During the same period, following daily stilbestrol administration, salpingitis was not present in any of 12 cases.

6. It is suggested that the estrogen-stimulated, thick, ciliated epithelium inhibits the spread of salpingitis during the proliferative and early secretory phases of the menstrual cycle.

References

1. Novak, E., and Everett, H. S.: Am. J. Obst. & Gynec. 16: 499, 1928.
2. Snyder, F. F.: Bull. Johns Hopkins Hosp. 35: 141, 1924.
3. Novak, E.: Gynecological and Obstetrical Pathology, Philadelphia, 1941, W. B. Saunders Company.
4. Sampson, J. A.: Am. J. Obst. & Gynec. 16: 743, 1928.
5. Connally, H. F., Jr.: Am. J. Obst. & Gynec. 46: 125, 1943.
6. Hellman, L. M.: Am. J. Obst. & Gynec. 57: 154, 1949.
7. Everett, H. S.: Am. J. Obst. & Gynec. 57: 164, 1949.
8. Hellman, L. M.: Personal communication.

PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA*

A Clinical Review of 340 Cases, Sloane Hospital for Women, 1933-1949

STANLEY M. BYSSHE, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and the Sloane Hospital for Women)

PREMATURE separation of the normally implanted placenta has long been recognized as a serious complication of pregnancy. As first defined by Rigby[1] in 1776 and Goodell[2] in 1875, this untoward development in a pregnancy carried a high mortality rate for both mother and fetus. The association of premature separation of the placenta with albuminuria, or toxemia, was portrayed by Chantreuil[3] in 1881. Their descriptions of this condition, and the "abruptio placentae" depicted by Holmes[4] in 1901, were undoubtedly limited to the gravest form of the complication. "Abruptio placentae," "ablatio placentae," and "accidental hemorrhage" have all been somewhat misleading terms. Fortunately, "premature separation of the normally implanted placenta" is now accepted, almost universally, as the all-inclusive term for the various forms of this mishap in pregnancy.

The etiology of premature separation of the placenta is still imperfectly understood; to date, investigators of the condition have not come into complete agreement. Due credit must be given for the extensive studies made by Young[5] in 1914, Williams[6] in 1915, Hofbauer,[7] in 1926, McKelvey[8] in 1939, Falkiner and Apthorp[9] in 1944, Bartholomew and associates[10] in 1948, and Sexton and collaborators[11] in 1948. The suggested underlying causes for premature separation of the placenta show these and other workers to be in partial or complete disagreement. Until a specific cause may be shown for at least the toxic type of premature separation of the placenta, we must continue to group together all forms of separation, whether associated with toxemia or not. One cannot ignore the cases of premature separation of the placenta brought about by the mechanical forces of trauma or labor, even though these cases may be relatively few in number and of little consequence.

In recent years, attempts have been made to classify the various types of premature separation of the placenta. The picture of this complication has grown to include the mildest form, where the clinical significance of the diagnosis may be tenuous; and the most severe form, endangering the life of a mother who already may have lost her baby in utero. Bartholomew,[12] Beavers,[13] Polak,[14] Dieckmann,[15] and Irving[16] have interpreted their cases with special reference to the clinical picture. The common association of at least the severe type of premature separation of the placenta with toxemia of pregnancy is an accepted fact. Any classification of premature placental separation must include an overlapping of the mechanical factors seen in some placental separations and the associated presence of toxemia. In many cases, if not properly in all, the classi-

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fication cannot be determined until after treatment has been instituted or the patient delivered. Of necessity, statistics for premature separation of the placenta, as reported from various clinics, are never quite in accord.

Material and Results

There were 340 cases of premature separation of the normally implanted placenta seen in 47,001 deliveries at the Sloane Hospital for Women in the years 1933 to 1949, inclusive. On the ward service there were 262 cases of premature placental separation in 29,480 deliveries, an incidence of 1 in 112. Since all private case histories were not available, the 78 cases found in private patients were not used in all the comparative statistics computed. All of the patients reported on were delivered in the viable premature and term periods, namely 28 to 40 or more weeks. The maternal mortality rate was 0.6 per cent, and the fetal mortality rate was 35.6 per cent.

It should be mentioned that practically all of the ward patients at the Sloane Hospital for Women are under medical surveillance from the earliest months of their pregnancies. It is also fair to state that in such pregnancy complications as toxemia, the milder cases are hospitalized for study. With premature separation of the normally implanted placenta, if our patients are not already hospitalized, there is no great delay before they are admitted when any untoward signs or symptoms occur. Thus the picture is one of fewer cases of untreated severe toxemia and fewer cases of premature placental separation made severe through delay. Unregistered patients are rare, and even some of the emergency admissions of these are of patients who have received prenatal care elsewhere.

This review of cases of premature separation of the placenta was made entirely on a clinical basis. The complication was classified (Table I) as mild, moderate, and severe, as suggested by Gustafson[18] and Sexton and associates.[11] All the cases had evidence of premature separation of the placenta in exhibiting adherent placental blood clots. The degree of separation, in most instances, has been evaluated according to the blood loss. In the group of severe cases, some did not have excessive bleeding, although the remaining qualifications of this group were met. The moderate type of separation, seen in about one-fourth of the patients, offered the most difficult evaluation. Undoubtedly, many of these cases could have been classified as severe. The mild cases represented two-thirds of the total, but were not thought to be insignificant, in view of the associated toxemia and fetal loss. Our classification made no allowance for the stage of labor. In the total number of ward deliveries, in the years reviewed, we saw 159 mild placental separations (an incidence of 1 in 185); there were 71 moderate separations (1 in 415); and there were 32 severe separations (1 in 921).

TABLE I. CRITERIA USED FOR CLASSIFICATION OF THE DEGREES OF PLACENTAL SEPARATION

A. Mild.—
Presence, clinically, of adherent blood clot involving no more than ⅙ of placental surface.
Total bleeding of less than 400 c.c.
No signs or symptoms of concealed hemorrhage.
B. Moderate.—
Presence, clinically, of adherent blood clot involving more than ⅙ but less than ⅞ of placental surface.
Total bleeding of more than 400 c.c., but not hemorrhagic.
Somewhat tense uterus.
C. Severe.—
Complete, or almost complete, involvement of placental surface.
Hemorrhagic bleeding, either concealed or manifest.
Uterus tense, tender, boardlike.
Varying degrees of shock.

Throughout the discussion of the cases herein reviewed, we have used the classification of toxemia of pregnancy set up by the American Committee on Maternal Welfare.[19] In the toxemia patients there was one case each of nephriits, pyelonephritis with hydronephrosis, and chronic hypertension. All three cases were considered to have a superimposed mild pregnancy toxemia. Only one eclamptic patient appeared in this series and she alone had oliguria following delivery.

Analysis of Material

The age of the patient had no bearing on her likelihood of encountering a premature separation of the placenta (Table II). Our patients with premature placental separations fell into the normal curve for ages of childbearing in general.

TABLE II. PREMATURE PLACENTAL SEPARATION, AGE GROUPS

SECOND DECADE 10-19	THIRD DECADE 20-29	FOURTH DECADE 30-39	FIFTH DECADE 40-49
17	185	128	10
Youngest patient 15			Oldest patient 45

This review showed that 162 patients were nulliparous and 178 were multiparous (Table III). In all deliveries over the same period, there was a ratio of 45 nulliparas to 55 multiparas. Thus parity played no part in placental separation.

TABLE III. PREMATURE PLACENTAL SEPARATION—PARITY

NULLIPARAS	MULTIPARAS
162	178

With premature separation of the placenta, the high incidence of viable prematures (28 to 37 weeks) was noted (Table IV). Viable prematures represented only 8.3 per cent of the total deliveries at Sloane Hospital for Women in the years reviewed, whereas with premature separation of the placenta 48.5 per cent of the cases were in this category.

TABLE IV. PREMATURE PLACENTAL SEPARATION, WEEKS OF GESTATION

VIABLE PREMATURE (28-37)	TERM (38+)
165	175

Toxemia.—With no accepted etiological factor for all premature separations of the placenta, we have analyzed our material with regard to pregnancy toxemia and other associated findings of possible importance. Toxemia of pregnancy was seen in 24.4 per cent of the cases with premature placental separations, as compared to toxemia in 12.4 per cent of all deliveries (Table V). In all ward deliveries in the period reviewed, the incidence of premature separation of the placenta in nontoxemia patients was 1 in 135, and in the toxemia patients was 1 in 51. We noted an associated toxemia once in 5.2 cases of mild placental separation, an associated toxemia once in 3.2 cases of moderate placental separation, and an associated toxemia once in 2.6 cases of severe placental separation. Thus it was concluded that not only was toxemia of pregnancy an important factor in premature separation of the placenta, but also the degree of placental separation increased in the presence of an associated toxemia. It was also observed that severe toxemia or eclampsia increased the likelihood of

the associated placental separation being severe. Some of the patients with severe premature separation of the placenta may have been in some degree of shock, and an associated toxemia was not apparent. This was true in one of our recent severe placental separations where only on the day following delivery did hypertension and albuminuria manifest themselves.

TABLE V. TOXEMIA OF PREGNANCY AND PREMATURE SEPARATION OF PLACENTA

	NO TOXEMIA	MILD PRE-ECLAMPSIA	SEVERE PRE-ECLAMPSIA	ECLAMPSIA	TOTAL
Mild separation	170	32	8	–	210
Moderate separation	61	22	5	–	88
Severe separation	26	7	8	1	42
Total	257	61 (17.9%)	21 (6.2%)	1 (0.3%)	340
Incidence of Toxemia 24.4%					

Associated Incidental Findings.—Other investigators have mentioned numerous incidental findings in patients with premature separation of the placenta. In this review, 23.2 per cent of the patients had such findings (Table VI). In these 79 cases the incidence of toxemia was quite equal to that for all placental separations, but only 3 severe cases of pre-eclampsia out of the 18 cases of toxemia were noted. The 61 cases without toxemia exhibited possible etiological factors in the placental separations in 17.9 per cent of the patients in this series. The high fetal mortality, 47.6 per cent, had to be attributed for the most part to the premature separation of the placenta. In the cases with a "short umbilical cord," the shortening was either true or relative. Under "trauma," only 4 patients had had falls, and this represented only 1.1 per cent of the total number of placental separations. Four patients encountered their trauma in versions or attempted versions. One had had an appendicectomy 36 hours before delivery, and one had had excessive pressure on the uterine fundus in a difficult breech delivery. In the cases with "hydramnios," the high fetal loss was explained in four of the babies by the congenital abnormalities. In the cases of "twins," where fetal losses were encountered, premature separation of the placenta was not the result of a version. The group of 7 "previous uterine operations" included 6 patients who had had previous cesarean sections. Only two cesarean sections were repeated for the placental separation and only one of the six babies was saved. The five fetal losses here were all in premature babies. In the cases of previous cesarean section, the placental separation in question may have resulted from a faulty attachment of the placenta over the uterine scar. The seventh patient had a cesarean section and living baby, after active labor pains had failed to move a rigid cervix that had been previously amputated. The cases with syphilis were included because this disease has been suspected of causing intrauterine death by premature placental separation. The patients with "fibroids" of the uterus all had sizable tumors. It was speculated that the tumors jeopardized the original attachment of the placenta or the maintenance of such attachment. Two other patients, not included above, had mild placental separations, one along with a resolving pneumonia and the other with mumps.

Early Antepartum Bleeding.—In 52 patients (15.3 per cent of our series of premature separations of the placenta there was a variable amount of bleeding in the earlier weeks of the antepartum period (Table VII). The bleeding in all of these patients occurred 24 or more hours before their deliveries. These cases were noted because an early partial separation seemed to have increased at delivery in some of them. While prematurity in the babies was increased, as

TABLE VI. PREMATURE SEPARATION OF PLACENTA INCIDENTAL FINDINGS OF POSSIBLE ETIOLOGICAL IMPORTANCE 79 CASES (23.2%)

	MILD SEPARATION	MODERATE SEPARATION	SEVERE SEPARATION	TOXEMIA 18 (22.7%)	FETAL LOSS
Short cord 28 (8.2%)	16	10	2	7	10
Trauma 10 (3.0%)	6	3	1	2	5
Hydramnios 7 (2.0%)	3	4	0	1	6
Twins 5 (1.4%)	1	3	1	2	4 of 10
Previous uterine operations 7 (2.0%)	2	3	2	1	5
Syphilis 11 (3.2%)	8	3	0	1	4
Fibroids 11 (3.3%)	5	5	1	4	6
Cases without toxemia 61 out of 340 (17.9%)					

TABLE VII. EARLY ANTEPARTUM BLEEDING IN PREMATURE SEPARATION OF PLACENTA (24 HOURS, OR MORE, BEFORE FINAL EPISODE) 52 CASES (15.3%)

EVENTUAL GESTATION	DEGREE OF SEPARATION	TOXEMIA (28.8%)	FETUS
Viable premature 33	Mild 36	Mild pre-eclampsia 11	Alive 37
Term 19	Moderate 12	Severe pre-eclampsia 3	Antepartum death 6
	Severe 4	Eclampsia 1	Intrapartum death 2
			Neonatal death 7

might be expected, the degree of placental separation, toxemia, and fetal loss were all about average for the whole series.

Repetition of Premature Placental Separation.—In this series of 340 cases, 14 patients had a repetition of premature separation of the placenta in a subsequent pregnancy. One patient had this diagnosis made in three successive pregnancies (Table VIII). While undoubtedly such a finding has been observed before, it has not been mentioned in the literature. Here again prematurity of the babies and associated toxemia appear as in the total series of placental separations, and fetal losses (38.7 per cent) were not appreciably higher. Two patients had mild separations repeated, no associated toxemia, and living babies each time. One nontoxemic patient had a severe type of separation treated by cesarean section the first time, and in the second pregnancy with a mild separation she was treated conservatively; both the babies survived. The one patient with three successive placental separations was never toxemic, always had a moderate or mild type of separation, was always treated conservatively, and only the first baby survived. One mildly toxemic patient with a uterus didelphys had mild placental separations at term at two deliveries. She was treated conservatively, and lost the first baby through intrapartum death and the second baby survived. Premature separation of the placenta suggests itself as a possible diagnosis for those rare patients who may lose their babies in utero in repeated pregnancies, where no other explanation has been offered.

Couvelaire Type of Uterus.—A Couverlaire type of uterus was described in only 14 cases (4.1 per cent of this series (Table IX). The description of the uterus as found at cesarean section in these cases varied from one of moderate ecchymosis of the myometrium to that of extensive hemorrhage into the uterine wall. Only five of the 14 patients had an associated pregnancy toxemia. In two cases, the placental separation was moderate only. Ten patients had the classical picture of pain and a tetanically contracted uterus. It was found necessary to do a hysterectomy in only one of the patients. The fetal mortality of 64.3 per cent in these patients reflected the gravity of the Couvelaire uterus. Our incidence of 44.4 per cent of Couvelaire uteri found at cesarean section for severe placental separation was appreciably lower than the 65 per cent reported by Eastman.[21] With this incidence of Couvelaire uterus in mind, it was assumed that no more than 44.4 per cent of the total of 42 severe placental separations

TABLE VIII. REPETITION OF PREMATURE SEPARATION OF PLACENTA, 15 PATIENTS (4.4%)

CASE	YEAR	DEGREE OF SEPARATION	TOXEMIA	TREATMENT	BABY	WEEKS OF GESTATION
1	1932	Mild	Mild	0	Intrapartum death	40
	1933	Mild	0	0	Alive	40
2	1933	Mild	0	0	Neonatal death	32
	1936	Mild	0	Conservative	Alive	33
3	1934	Moderate	0	Conservative	Neonatal death	32
	1935	Moderate	0	Conservative	Alive	36
4	1935	Moderate	0	0	Alive	40
	1940	Mild	0	Conservative	Neonatal death	33
	1946	Moderate	0	0	Intrapartum death	38
5	1932	Mild	0	0	Alive	40
	1936	Mild	0	Conservative	Antepartum death	40
6	1924	Mild	0	0	Alive	40
	1936	Mild	Mild	0	Alive	40
7	1936	Moderate	0	0	Neonatal death	30
	1938	Mild	0	Conservative	Alive	40
8	1936	Mild	0	0	Alive	40
	1940	Mild	0	0	Alive	40
9	1937	Mild	0	0	Alive	36
	1946	Mild	0	0	Neonatal death	32
10	1939	Mild	0	Conservative	Alive	40
	1945	Mild	0	0	Alive	40
11	1941	Severe	0	Cesarean	Alive	37
	1944	Mild	0	Conservative	Alive	37
12	1942	Mild	Mild	0	Alive	35
	1945	Mild	0	0	Alive	40
13	1943	Mild	0	Cesarean	Alive	40
	1945	Moderate	0	Conservative	Intrapartum death	40
14	1945	Mild	0	Conservative	Neonatal death	32
	1946	Moderate	0	0	Neonatal death	28
15	1947	Severe	Severe	Cesarean	Intrapartum death	34
	1949	Severe	Mild	Conservative	Intrapartum death	28

in our series had a Couvelaire type of uterus. Certainly a tonic uterus and concealed bleeding did not necessarily result in a Couvelaire uterus, as has been suggested by other observers. Both the tonic uterus and concealed bleeding were noted by us to occur as often in the mild and moderate placental separations as in the severe cases. Actual growth of the uterus was noted in only two severe cases in the entire series, so that this sign could not be considered to be too important.

TABLE IX. COUVELAIRE TYPE OF UTERUS IN PREMATURE SEPARATION OF PLACENTA
14 CASES (4.1%)

	TYPE OF SEPARATION		
	MILD	MODERATE	SEVERE
No toxemia	0	2	7
Mild Pre-eclampsia	0	0	1
Severe Pre-eclampsia	0	0	3
Eclampsia	0	0	1
Fetus Alive (35.7%).—			
Premature	0	2	1
Term	0	0	2
Fetus Dead (64.3%).—			
Premature	0	0	7
Term	0	0	2

Bleeding in Premature Separation of the Placenta

The literature constantly refers to the danger of postpartum hemorrhage in patients with premature separation of the placenta. The incidence of postpartum hemorrhage for all deliveries at Sloane Hospital for Women, in the years reviewed, was 4.6 per cent. In this series, excessive bleeding (500 c.c. or more) was seen in and about the third stage of labor in 34 (10 per cent of the cases. No further hemorrhagic bleeding occurred at a point later in the postpartum period of the patients delivered vaginally. In the cesarean section patients there were none who bled excessively after the closure of the uterus. The one exception to this was in a multipara who had had a previous cesarean section done at another hospital for placental separation. In her repeat episode, at this hospital, of a moderate premature separation of the placenta she was treated conservatively. Because of continued postpartum bleeding and later shock, hysterectomy was performed 36 hours post partum for rupture of the uterus. In all of the 340 cases presented, 80 patients (23.5 per cent) were transfused. In this series of premature separations of the placenta there were no cases of exsanguination or other clinical evidence suggesting the blood coagulation defects reported by Sexton[11] and Weiner[24] and their associates.

Pathology

In our series of cases, no special pathology study was made of the numerous placentas or the few available uteri. Most placentas from cases of severe separation or severe toxemia were examined routinely in the pathology laboratory. In general the reports were those of red or white infarction of the placenta, placental hematoma, or necrosis of the placenta. Three specimens of succenturiate lobe, two circumvallate placentas, and one erythroblastotic placenta were encountered. The two circumvallate placentas are strikingly few compared to the 88 such placentas reported by Sexton and collaborators[11] in their 476 cases of premature separation of the placenta. Rupture of the marginal sinus of the placenta was an infrequent finding.

Treatment

Individualization of treatment for each case was the course followed in the care of our 340 patients with premature separation of the placenta. Throughout the literature the term "conservative treatment" for this complication applies to vaginal delivery, and cesarean section is reserved for the remaining patients. No specific treatment was offered to 165 (48.4 per cent) of our patients with premature placental separations. Most of these patients had a mild type of separation and the diagnosis was usually made by postpartum inspection of the placenta. Where the diagnosis of moderate or severe placental separation was considered early, the patient's general condition was taken into consideration with regard to amount of bleeding, toxemia, and shock. When labor was efficient, and a favorable cervix present, and expected delivery not too distant, the patient was allowed to deliver vaginally. Here the membranes were ruptured artificially and delivery hastened with forceps after full dilatation of the cervix. Cesarean section was done frequently in the interests of the fetus in severe placental separations or where there was evidence of fetal distress in the less serious cases. In many patients, cesarean section seemed to be indicated in the presence of a dead baby in utero, when the apparent degree of placental separation warranted abdominal hysterotomy to check the bleeding and prevent further and prolonged shock. Oxytocics, bags, and binders were rarely used, while the cervix and vagina were never packed to hasten labor. In two patients, after artificial rupture of the membranes had failed to produce efficient labor, Pitocin

was used. In the resulting tetanically contracted uteri and placental separations, either development may have been the direct result of the use of Pitocin. Internal podalic version was done once for a transverse presentation and once for the second of twins.

In the 165 patients who were offered no specific treatment (Table X), a premature placental separation was merely suspected in labor or not diagnosed until after delivery. These patients represented the cases of placental separation of little clinical significance. The fetal mortality for this group (30.9 per cent) certainly left room for improvement through more careful intrapartum observation and effort to deliver some of the babies with less delay. The two severe cases which received no specific therapy occurred in nontoxic multiparas in advanced labor with unsuspected concealed hemorrhage; their babies were both lost in labor.

TABLE X. EXPECTANT TREATMENT (NONE) IN PREMATURE SEPARATION OF PLACENTA

CASES	TOXEMIA	TYPE OF SEPARATION			FETAL LOSS
		MILD	MODERATE	SEVERE	
165 (48.4%)	42 (25.4%)	123	40	2	51 (30.9%)

The analysis of our conservative treatment of premature separation of the placenta versus cesarean section (Table XI) revealed a somewhat higher fetal loss in the patients with associated toxemia. Cesarean section, in the years reviewed, was used for 5.2 per cent of all deliveries, whereas this operation was done for 12.9 per cent of the cases with premature placental separation. Associated toxemia of pregnancy, especially severe toxemia, was somewhat more prevalent in the cases treated by hysterotomy, 32 per cent of the cesarean sections being in patients with toxemia. One unsuspected mild premature separation of the placenta was found at the time of an elective cesarean section being done for disproportion. Since one mother was lost following each type of treatment, the maternal mortality rate was 2.3 per cent for cesarean section and 0.34 per cent for conservative treatment.

TABLE XI. ANALYSIS OF TREATMENT IN PREMATURE SEPARATION OF PLACENTA

	NO TOXEMIA (75.6%)		TOXEMIA (24.4%)	
	DELIVERIES	FETAL LOSS	DELIVERIES	FETAL LOSS
Conservative (87.1%)	226	74	70	27
Cesarean (12.9%)	30	10	14	10
Total	256	84 (32.8%)	84	37 (42.8%)

Maternal Mortality

The gross maternal mortality figure was 0.6 per cent in this series of 340 cases of premature separation of the placenta. The two maternal deaths resulted from severe placental separations in patients with severe pre-eclampsia. The corrected mortality rates were 4.7 per cent for our severe type of premature separation of the placenta in general, and 9.0 per cent for our patients with any premature separation of the placenta associated with severe pre-eclampsia and eclampsia. Barrett[20] showed a maternal mortality rate of 1.3 per cent in a series similar to ours, where there were many mild placental separations included. Hudnall and co-workers[23] quoted 3.4 per cent for their maternal mortality. Eastman[21] stated that concealed hemorrhage, along with shock and the amount of

blood loss, was the determining factor in the prognosis for premature separation of the placenta. Since both of our maternal deaths were in patients with no concealed hemorrhage, we had the single figure of 0.6 per cent maternal mortality for cases with manifest hemorrhage. At the New York Lying-In Hospital,[21] the mortality rate was reported as 1.1 per cent for external hemorrhage and 9.1 per cent for concealed hemorrhage. In a similar analysis, Irving[22] had figures of 1.7 per cent maternal mortality for external bleeding and 11.8 per cent for concealed bleeding. In our series, the maternal mortality for vaginal deliveries was 0.34 per cent, and for cesarean sections was 2.3 per cent. Again, Hudnall and associates[23] gave figures of 14.7 per cent for vaginal deliveries and 4.0 per cent for their cesarean sections. In reporting a smaller series of placental separations, Gustafson[18] had no maternal deaths.

Maternal Deaths

CASE 1.—A 36-year-old gravida xi, para x, who had a premature separation of the placenta in her two final pregnancies, was not toxemic in the first case and lost her premature baby after conservative therapy. Then, in her final admission in 1935, she developed a severe pre-eclampsia and severe placental separation and the baby succumbed in utero. A cesarean section was done and a mild degree of the Couvelaire type of uterus was noted. She died of pneumonia on the fourth postoperative day.

CASE 2.—A 20-year-old gravida i was admitted in 1942 in the thirty-sixth week of her pregnancy. She had a severe pre-eclampsia and a severe degree of placental separation. Treatment consisted of artificial rupture of the membranes, followed by delivery of a fetus which had died intra partum. After a 1,000 c.c. transfusion she developed ventricular fibrillation and died 10 hours post partum in unrelieved shock.

These two maternal deaths may have been preventable in light of our present use of antibiotics, and of better knowledge and facilities for the treatment of severe shock.

Fetal Mortality

The gross fetal mortality in our series of cases with premature separation of the placenta was 35.6 per cent (Table XII). There were five sets of twins which added five additional babies that encountered the complication of premature placental separation. There was a fetal loss of 67.4 per cent in the severe separations, 45.1 per cent in the moderate separations, and 19.1 per cent in the mild separations.

TABLE XII. FETAL LOSS IN PREMATURE SEPARATION OF PLACENTA

	PREMATURE			TERM		
	MILD SEPARATION	MODERATE SEPARATION	SEVERE SEPARATION	MILD SEPARATION	MODERATE SEPARATION	SEVERE SEPARATION
Alive 224	59	14	5	100	37	9
Antepartum death 39 (11.4%)	5	11	10	4	3	6
Intrapartum death 39 (11.4%)	6	7	9	6	8	3
Neonatal death 43 (12.8%)	24	10	0	5	3	1
Fetal Loss 121 (35.6%)						

Analysis of results for the baby in cases with associated toxemia (Table XIII) showed a fetal mortality of 44.5 per cent, and in patients without toxemia the fetal mortality was 32.7 per cent. Antepartum, intrapartum, and neonatal

deaths were equally distributed throughout the fetal deaths in the entire series. Roughly two-thirds of all the fetal deaths were in viable premature babies. When the antepartum fetal deaths were excluded, the results improved equally whether conservative treatment or cesarean section was used, giving a corrected figure of 24.2 per cent for the remaining babies that conceivably could have been saved.

TABLE XIII. FETAL LOSS IN PREMATURE SEPARATION OF PLACENTA AND RELATED TOXEMIA

	PREMATURE 165		TERM 175	
	NO TOXEMIA	TOXEMIA	NO TOXEMIA	TOXEMIA
Alive 224	65	13	112	34
Antepartum death 39 (11.4%)	15	11	11	2
Intrapartum death 39 (11.4%)	10	12	12	5
Neonatal death 43 (12.8%)	28	6	8	1

In the study of fetal deaths occurring in the cesarean sections performed (Table XIV), it was apparent that most of the fetal losses were in patients with more serious placental separation and more serious toxemia. The fetal loss of 45.4 per cent in the cesarean sections probably could not have been reduced, except possibly through the earlier election of the operation in some cases.

TABLE XIV. FETAL STATISTICS—CESAREAN SECTIONS—PREMATURE SEPARATION OF PLACENTA

	NO TOXEMIA				TOXEMIA			
TYPE OF SEPARATION	ALIVE	ANTE-PARTUM DEATH	INTRA-PARTUM DEATH	NEONATAL DEATH	ALIVE	ANTE-PARTUM DEATH	INTRA-PARTUM DEATH	NEONATAL DEATH
Mild 10 (22.7%)	6			1	2			1
Moderate 7 (16.0%)	5			1		1		
Severe 27 (61.3%)	9	6	1	1	2	4	4	
Total	20	6	1	3	4	5	4	1
Fetal Loss 45.4%								

TABLE XV. INTRAPARTUM DEATH OF FETUS IN PREMATURE SEPARATION OF THE PLACENTA

	CONSERVATIVE TREATMENT			CESAREAN SECTION		
	NO TOXEMIA	MILD PRE-ECLAMPSIA	SEVERE PRE-ECLAMPSIA	NO TOXEMIA	MILD PRE-ECLAMPSIA	SEVERE PRE-ECLAMPSIA
Mild Separation	11	2				
Moderate Separation	8	4	2			
Severe Separation	2	2	3	1	1	3*

*Includes 1 case of eclampsia.

Intrapartum Fetal Death.—A further study of the 39 intrapartum fetal deaths in cases of premature separation of the placenta was made (Table XV). In the intrapartum deaths, 56.4 per cent of the babies were viable prematures. With due consideration for the condition of the mother, intrapartum fetal deaths might have been reduced considerably by expediting delivery. With the intrapartum deaths in cesarean sections, the placental separations were all severe and toxemia was usually present. These babies apparently stood little chance of

survival. Probably the same was true for the babies in cases where severe placental separation was treated conservatively. There were 25 babies (20 per cent of all fetal deaths) who died intra partum whose mothers exhibited only mild or moderate placental separation along with only mild pre-eclampsia or no toxemia. Here, delivery at an earlier moment certainly would have saved a high percentage of these 25 babies.

Summary and Conclusions

During the 17-year period, 1933-1949, 340 cases of premature separations of the normally implanted placenta occurred in 47,001 deliveries at the Sloane Hospital for Women. These cases were classified, and then studied with regard to associated toxemia and other possible etiological factors. Treatment, maternal mortality, and fetal mortality were appraised.

1. A clinical classification of premature separation of the placenta was used. On the ward service there were 159 mild separations (1 in 185), 71 moderate separations (1 in 415), and 32 severe separations (1 in 921).

2. Premature separation of the placenta was associated with the deliveries of a high incidence of viable premature babies (48.5 per cent of the cases).

3. In 52.4 per cent of the premature placental separations there was no associated cause noted; in 24.4 per cent, various degrees of pregnancy toxemia were present; in 23.2 per cent, a group of associated incidental findings was seen.

4. In 4.4 per cent of the premature separations of the placenta, this complication was a recurrence in the same patient in a different pregnancy.

5. Treatment for premature separation of the placenta was that of individualization for each case. In the conservatively treated group, 48.4 per cent of all cases had been given no specific treatment whatsoever. Cesarean section was done in 12.9 per cent of the cases in the series.

6. The gross maternal mortality rate for the series was 0.6 per cent. This figure was corrected to 9.0 per cent for the patients with premature placental separations and associated severe toxemia. In the light of present-day methods, the two maternal deaths might have been prevented.

7. The fetal mortality rate was 35.6 per cent for the entire series of premature separations of the placenta. Where premature placental separation and toxemia were associated, the fetal mortality rate was 44.5 per cent. In the cases of severe placental separation the fetal mortality rate was 67.4 per cent.

8. Special note was made of the cases of intrapartum fetal death seen in premature separation of the placenta. Twenty-five babies (20 per cent of all the fetal deaths encountered) might have been saved by more radical treatment, either through less delay in vaginal delivery or by the earlier election of cesarean operation.

References

1. Rigby, E.: In Williams, J. W.: Surg., Gynec. & Obst. 21: 541, 1915.
2. Goodell, J. R.: In Sexton, L. I., Hertig, A. T., Reid, D. E., Kellogg, F. S., and Patterson, W. S.: Am. J. Obst. & Gynec. 59: 13, 1949.
3. Chantreuil, G.: In Irving, F. C.: Outline of Abnormal Obstetrics, Ann Arbor, Mich., 1944, Edwards Bros., Inc.
4. Holmes, R. W.: In Kellogg, F. S.: Am. J. Obst. & Gynec. 15: 357, 1928.

5. Young, J.: J. Obst. & Gynaec. Brit. Emp. 26: 1, 1914, and 34: 279, 1927.
6. Williams, J. W.: Surg., Gynec. & Obst. 21: 541, 1915.
7. Hofbauer, J.: Am. J. Obst. & Gynec. 12: 159, 1926.
8. McKelvey, J. L.: Am. J. Obst. & Gynec. 38: 815, 1939.
9. Falkiner, N. M., and Apthorp, J. O. E.: J. Obst. & Gynaec. Brit. Emp. 51: 30, 1944.
10. Bartholomew, R. A., Colvin, E. D., Grimes, W. H., Jr., and Fish, J. S.: Am. J. Obst. & Gynec. 57: 69, 1949.
11. Sexton, L. I., Hertig, A. T., Reid, D. E., Kellog, F. S., and Patterson, W. S.: Am. J. Obst. & Gynec. 59: 13, 1949.
12. Bartholomew, R. A.: In Odell, L. D., and McDonald, D. F.: Am. J. Obst. & Gynec. 56: 74, 1948.
13. Beavers, H.: Texas State J. Med. 33: 28, 1937.
14. Polak, J. O.: Am. J. Obst. & Gynec. 7: 384, 1924.
15. Dieckmann, W. J.: In Irving, F. C.: Internat. Obstr. Surg. 67: 56, 1938.
16. Irving, F. C.: Internat. Abstr. Surg. 67: 56, 1938.
17. McCord, J. R.: In Miller, J. R.: Am. J. Obst. & Gynec. 42: 754, 1941.
18. Gustafson, G. W.: Am. J. Obst. & Gynec. 49: 103, 1945.
19. American Committee on Maternal Welfare: The Mother 1: 14, 1940.
20. Barrett, R. L.: Clinics 4: 1055, 1945.
21. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, D. Appleton-Century Company.
22. Irving, F. C.: In Eastman, N. J.: Williams Obstetrics, New York, 1950. D. Appleton-Century Company.
23. Hudnall, H. W., Jr., Winn, W. C., and Schelin, E. C.: South. M. J. 37: 163, 1944.
24. Weiner, A. E., Reid, D. E., and Roby, C. C.: Am. J. Obst. & Gynec. 60: 379, 1950.

Discussion

DR. RALPH L. BARRETT.—We should recognize that some obstetricians are inclined to select the so-called conservative treatment in the management of premature separation of the placenta. These obstetricians elect to manage the condition by vaginal delivery. By so doing, these obstetricians not infrequently watch a mild or moderately severe instance of premature separation progress and become a really severe case of ablatio placentae during this time of conservative management.

For this reason, many of us have elected the apparently more radical treatment of the condition. If signs and symptoms indicate a premature separation of the placenta, supportive treatment of plasma, blood, etc., is indicated and instituted, plus sufficient sedation to control pain. Then a careful evaluation of the patient is made. This includes special attention to the condition of the cervix as to dilatation, consistency and retraction, the viability and condition of the baby, as well as the general factors concerning the mother. If delivery is not imminent and it appears that labor will be prolonged over several hours with inevitable added danger to the baby as well as the almost certain progression of both visible and concealed hemorrhage, then cesarean section is selected.

By this method of treatment at the Woman's Hospital, we have very definitely lowered the fetal and maternal mortality attributable to premature separation of the placenta.

DR. S. A. COSGROVE.—It is very difficult to assimilate all of these data. Many of the cases which Dr. Bysshe has defined as mild can be dismissed as of minor clinical importance. Some of them do go on progressively to much more serious types. If one in watching these milder cases appreciates such progression, then more radical treatment not only conserves fetal but the mother's life, in that it anticipates the development of most serious pathology in the mother herself. I think that there can be no hard and fast adherence of one's allegiance to conservative treatment or radical treatment. Conservative treatment is probably recognized as applicable to nearly all the cases of the mild group and to a large number of the moderate group. We ourselves believe quite definitely in the application of radical treatment to the severe group. In addition, there is a borderline group of progressive clinical development under observation, which I think had better be treated radically to insure the optimal fetal and maternal results.

DR. E. E. BUNZEL.—With accidental hemorrhage the type of uterus encountered at the time of cesarean often shows marked areas of hemorrhage in the musculature. Several

years ago we were all advised to remove such a uterus not only because of the great possibility of postpartum hemorrhage but also because of the likelihood of infection. Today, however, there seems to have been a change in attitude in the treatment of this type of uterus. I should like to hear some opinions from members of other hospital staffs as to what they feel should be done with this type of uterus.

DR. GORDON DOUGLAS.—It would be necessary for me to study these data presented by Dr. Bysshe before I could make any comparison with our experience in the New York Lying-In Hospital. It was my impression that the problem of whether the uterus should be removed following delivery of the infant by cesarean section was settled at least 35 years ago. Irrespective of its appearance or the degree of hemorrhage in the uterine wall, the organ is removed only when it fails to function (contract) in a reasonably satisfactory manner.

Our experience in common with that of the essayist indicates that, even if there is extensive hemorrhagic extravasation, it is only on the rarest occasion that hysterectomy because of uterine atony becomes necessary.

DR. S. A. COSGROVE.—I quite agree with what Dr. Douglas said about the safety of leaving the uterus depending on obvious functional capacity to contract rather than upon the extent of discoloration. In our experience it has been many years since we have done a primary hysterectomy for abruption of the placenta. I recall just now only one case in which, after failure to do a primary hysterectomy, it was necessary to do one secondarily for continued uterine bleeding.

DR. R. S. MILLEN.—I would like to ask two questions. Do you mean by your remarks under treatment: "rupture of the membranes and forceps delivery at full dilatation," that you do both procedures at that time, rather than rupture the membranes as soon as the diagnosis is made in the suitable case for such a procedure, and then forceps delivery at full dilatation?

Second, do you ever consider elective rupturing of the membranes in the patient with a favorable cervix, at or near term, who has a history of a stillbirth from premature separation of the placenta in the previous pregnancy?

DR. LOUIS HELLMAN.—There are two points, which are of great interest to me. The first is the question of the removal of the Couvelaire uterus because of its failure to contract. In spite of the gross hemorrhage, postpartum atony is extremely rare in this condition. I think a more careful study of microscopic sections from these uteri will reveal the reason for this. There is very little actual muscle damage. The hemorrhage is in the interstices between the muscle bundles. It would be of advantage to know the exact source of this bleeding. In studying a number of patients for sterility, using the injection of methylene blue and viewing the tubes through a culdoscope, we were struck by the fact that the methylene blue frequently appeared beneath the peritoneal covering of the uterus. It is my opinion that this methylene blue was carried in the lymphatics and that the same is true in the case of blood and the Couvelaire uterus. The blood is not due to rupture or to abnormalities of the deep uterine vessels but is due to lymphatic absorption of retroperitoneal blood and possibly to rupture of lymphatics. This would explain the presence of blood beneath the peritoneum of the broad ligament and would also indicate why the majority of these uteri contract in a normal fashion during the post partum period. The second point of interest is the study of the cases which Dr. Bysshe has termed "mild." It is usual to devote most attention to the severe cases for these are the most striking and do carry a definite maternal mortality. However, the mild cases have an extremely high fetal mortality rate. It is in this group that marginal separation with rupture of the marginal sinus occurs. This entity has received little attention and deserves very careful study. Separation of the margin of the placenta interrupts the whole venous drainage of this organ and probably throws out of balance the hemodynamic exchange between mother and fetus. It is for this reason that an extremely high infant death rate is associated with this lesion. The only possibility of reducing this high rate is by prompt delivery. Whether we will be

able to diagnose this type of antepartum hemorrhage with a sufficiently high degree of accuracy to enable us to do cesarean section in these cases is a moot question. It is, however, my opinion that the day will come when many more sections are done for antepartum hemorrhage than we now consider justifiable.

DR. BYSSHE (Closing).—I would like to apologize for presenting a paper that is so difficult to follow because of the many numerical statistics quoted. I tried to emphasize the fact that 20 per cent of all of the fetal losses encountered were intrapartum fetal deaths, and, therefore, should be considered as possibly preventable. This is more especially true since these losses occurred in 25 cases of mild or moderate placental separation, where associated toxemia was either insignificant or nonexistent. Since all of these cases were treated conservatively, the fetal losses might have been erased by earlier recognition of the complication and more expeditious treatment. The use of more cesarean operations may be the answer, for certainly fetal outcome should assume more importance in this complication.

There has been no definite trend toward more cesarean sections for this complication. Cesarean section is being done at the Sloane Hospital for Women somewhat more often for moderate placental separations, apparently in the interests of the baby. Cesarean sections were too few to offer a significant year-by-year analysis of the results.

In the cases of severe placental separation treated by cesarean section, a Couvelaire type of uterus was noted in 44.4 per cent of the patients. It can be assumed that the Couvelaire uterus may have been present in 44.4 per cent of all the cases classified as severe, whether treated conservatively or by cesarean section. Hysterectomy was done but once in the 14 known cases of Couvelaire uterus. In none of the severe separations did the uterus react abnormally in the postpartum period.

Where the diagnosis of premature placental separation was made and vaginal delivery elected, various methods of hastening labor and delivery were used. Pitocin infusion was used in one patient not appearing in the series, since she was only six months pregnant. Here the infusion failed to produce labor. Two patients were also mentioned who had received Pitocin in the elective induction of labor. These two patients developed premature separation of the placenta that may have been the result of the use of Pitocin, since the ensuing tetanically contracted uteri may have caused the placental separations.

DR. MILLEN.—I understand that you spoke about rupture of the membranes and then delivery in the conservative type of treatment.

DR. BYSSHE.—Artificial rupture of the membranes was frequently used to induce or hasten labor where conservative treatment was elected. After due labor and full dilatation of the cervix, forceps were occasionally used in the interests of the baby. I would not hesitate to rupture electively the membranes in a patient with a favorable cervix at term, who had had a previous stillbirth resulting from premature separation of the placenta. Many spontaneous deliveries were done in unsuspected premature placental separations, and some of these babies succumbed late in labor. Again, I would like to emphasize that earlier diagnosis and earlier delivery in these seemingly insignificant placental separations would save many babies.

PROLAPSE OF THE CORD DURING LABOR

ARNOLD N. FENTON, M.D., AND D. ANTHONY D'ESOPO, M.D., NEW YORK, N. Y.

(From the Sloane Hospital for Women)

PROLAPSE of the umbilical cord is not a common obstetrical complication, yet it is encountered with sufficient frequency and the fetal end results are generally so poor that it becomes an important subject for consideration. Although the associated fetal mortality has always been reported to be very high,[1] it appears that more recent experience in our clinic indicates some improvement. For this reason, this analysis of 216 cases of prolapsed cord which occurred during a period of twenty-five years was made, with special interest directed toward a comparison of five-year intervals to determine, if possible, the reasons for the better fetal salvage rate. Included in the series are the seventy-one cases reported previously by Gusberg[2] from our service.

The literature and standard texts do not agree on the criteria for defining the degrees of prolapse of the umbilical cord and the related condition, cord presentation. We have defined prolapse of the umbilical cord as a condition in which the cord lies below both the pelvic inlet and the presenting lower fetal pole. Partial prolapse exists when the cord can be palpated below the pelvic inlet but remains above the lowermost part of the presenting fetal pole. In cord presentation, the cord lies above the pelvic inlet and at or below the presenting fetal pole.

Material

Prolapse of the cord occurred 216 times in 60,788 deliveries from 1924 through 1948, an incidence of 0.35 per cent or 1:281 deliveries. Prior to 1916, Cragin[3] reported 269 cases in 20,000 deliveries or 1.3 per cent at the Sloane Hospital. This figure is similar to that noted in other reports.[4, 5] Cases of partial prolapse are included for they present essentially the same problems and are accompanied by a significantly high fetal mortality. Cases of prolapse occurring when the fetus weighed under 2,000 grams have been excluded because immaturity as a cause of death enters to such an extent that an evaluation of fetal end results in reference to therapy becomes unnecessarily complicated.

There has been no striking change in incidence throughout this period although there is some tendency for the condition to become somewhat less common in recent years (Table I). A probable explanation is the fact that cephalopelvic disproportion, one of the etiological factors in prolapse, has been more frequently treated by cesarean section.

Fetal Mortality Rate.—The gross and corrected fetal mortality rates are noted in Table II. It is apparent that even when all possible corrections are made to convert the fetal group to one that can be considered entirely salvageable, the mortality remains about 30 per cent.

When the gross and corrected fetal mortalities are analyzed for each five-year period (Fig. 1), we find that our initial impressions of a recent decline in the fetal mortality are correct. Both the gross and corrected mortalities show an improvement of 25 and 30 per cent, respectively.

TABLE I. INCIDENCE

		CASES	DELIVERIES	INCIDENCE
Group I	1924-1928	36	8,524	1:236
Group II	1929-1933	44	11,778	1:267
Group III	1934-1938	40	11,793	1:294
Group IV	1939-1943	43	13,078	1:304
Group V	1944-1948	53	15,615	1:294
Total		216	60,788	1:281

TABLE II. INFANT MORTALITY

	CASES	DEATHS	FETAL MORTALITY PER CENT
Total uncorrected	216	81	37.5
Corrected for 16 cases prolapsed at home, leaving	200	66	33.0
Corrected for 2 congenital defects incompatible with life, leaving	198	64	32.3
Corrected for 18 infants under 2,500 grams, leaving	180	55	30.5
Corrected for 7 cases of premature separation of placenta, leaving	173	52	30.0
Corrected for 4 cases of placenta previa, leaving	169*	49	28.9

Etiology.—Related studies[1, 6] have emphasized the fact that abnormal presentation is probably the greatest single predisposing factor, a fact with which we agree (Table III). It is interesting to find that obstetrical manipulations account for 15 per cent of these cases, which concurs with other reported data.[5, 7] Of the 30 cases in the latter group, 25 were caused by artificial rupture of the membranes when the presenting part was not engaged and the remaining 5 were due to manual elevation of the vertex when rotation above the pelvic brim was attempted.

TABLE III. ETIOLOGY

POSSIBLE PREDISPOSING FACTORS	NO. OF CASES	INCIDENCE PER CENT
1. Presentation, fetal	77	35.8
2. Spontaneous rupture with high fetal head	35	17.5
3. Obstetrical manipulations	30	15.
4. Cephalopelvic disproportion	24	12.
5. Multiple pregnancies	20	10.
6. Pelvic tumor	13	6.5
7. Abnormal placentation	11	5.5
8. Hydramnios	10	5
9. Long cord	5	2.5
10. Abnormal uterine axis*	3	1.5
11. Excessive straining	1	0.5
12. Unknown	51	25.6

*Abnormal uterine axis includes: uterine suspension, ventral hernia, and pendulous abdomen.

Prolapse occurred in 20 instances of twin pregnancies. The cord of twin A was involved 11 times with a fetal mortality of 72.7 per cent while that of twin B prolapsed 9 times with a fetal mortality of only 11.1 per cent. The difference in these rates is due to the fact that the prolapse of the cord of the second twin occurred under ideal circumstances. The diagnosis was made early and, with a fully dilated cervix, delivery was effected without delay. The high salvage rate for twin B bears out the importance of early diagnosis combined with effective treatment.

Parity.—In this series 128 patients, or 59.2 per cent, were multiparas. This figure does not show any appreciable difference from the hospital incidence of multiparous labors for the past fifteen years which was 54 per cent. Although it has been reported that the fetal mortality rate in primigravidas is almost twice that in multigravidas,[8] our series did not show this difference, the fetal mortality being 29.2 per cent for primigravidas and 38.1 per cent for multigravidas.

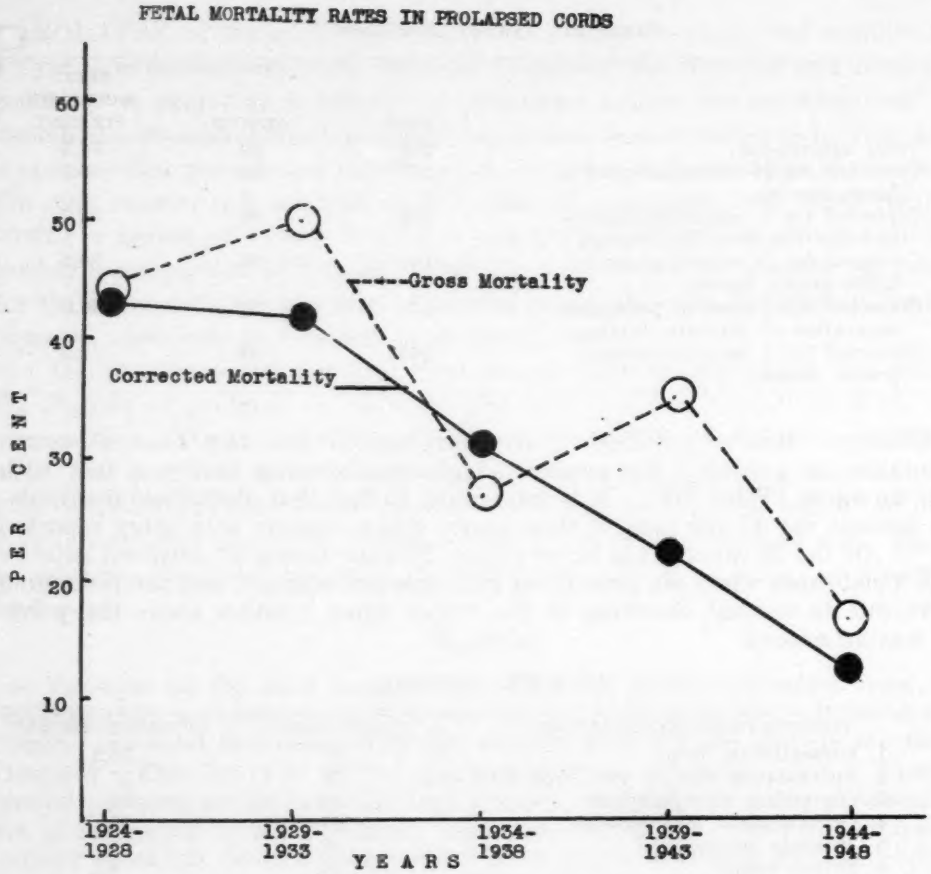

Fig. 1.

Pelvis.—The variations in the size and shape of the pelvis per se seem to be unrelated to the etiology of this complication for there was not a disproportionately high incidence of any particular type of pelvis in this group when compared to the average distribution of pelvic types. Whether or not there was a higher incidence of disproportion between the presenting part and the inlet when compared to that of the total delivered group, is not ascertainable from the data. The fetal mortality, however, showed a definite increase with pelvic contraction,[9] which is understandable, since rapid delivery through such pelves superimposes the risk of trauma upon the existing problem of anoxia.

Presentation.—The distribution of the various types of presentations is shown in Table IV. When these figures are compared to the average incidence, the disproportionately large number of breech, transverse, face-brow, and compound positions is striking. Since these presentations are most frequently as-

sociated with maladaption of the presenting part to the pelvic inlet, we have here the most significant etiological factor for this condition.

It has been said that the fetal mortality is highest in vertex presentations because of the greater danger of cord compression.[5] Our data do not agree with this and, when they are analyzed, it is found that prolapsed cord in vertex presentations was frequently due to obstetrical manipulations such as artificial rupture of the membranes with high head, and manual rotation of the vertex with upward displacement of the vertex. Diagnosis was made early and, the

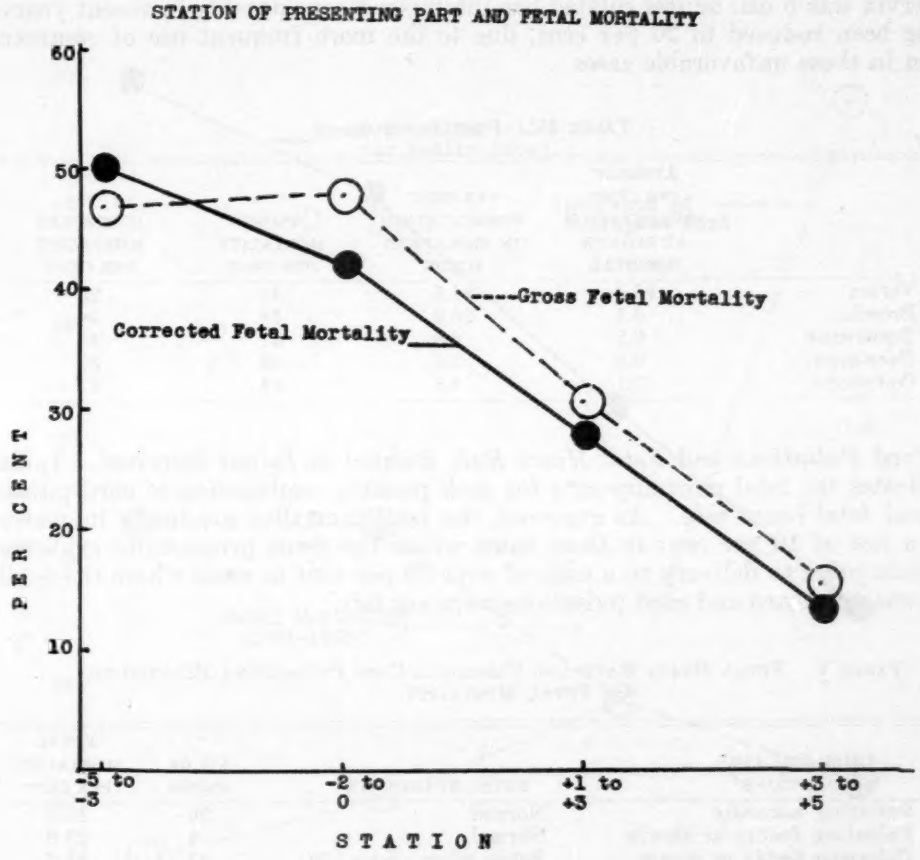

Fig. 2.

cervix being fully dilated in most instances, permitted prompt delivery with a high salvage rate. These favorable conditions more than compensated for the greater compression of the cord by the vertex which is usually offered as an explanation for the high fetal mortality in vertex presentations.

Station of the Presenting Part.—The station of the presenting part at the time of diagnosis that was most frequently noted was 1 to 3 cm. below the level of the spines. Since it is assumed that the prolapse generally occurs when the presenting part is unengaged, we must conclude that a delay in making the diagnosis is not uncommon. Approximately two-thirds of the cases were diagnosed after engagement of the presenting part had taken place.

As shown graphically in Fig. 2, there appears to be a direct relationship between the level of the station and the fetal mortality.

When analyzed according to groups, it is found that at station minus 5 to zero, for the years 1924-1943, the fetal mortality was 54 per cent while during the years 1944-1948 for the same station the fetal mortality rate was less than half, or 21 per cent. This will be discussed further.

Cervix.—It is evident (Fig. 3) that there is an inverse relationship between fetal mortality and dilatation of the cervix at the time of cord prolapse. There is also a greater incidence of prolapse as the cervical dilatation increases, with a peak incidence when the cervix is fully dilated.

The extremely high fetal mortality in the cases of prolapse occurring when the cervix was 5 cm. or less dilated has diminished considerably in recent years, having been reduced to 20 per cent, due to the more frequent use of cesarean section in these unfavorable cases.

TABLE IV. PRESENTATION

	AVERAGE PER CENT PRESENTATION AT SLOANE HOSPITAL	PER CENT PRESENTATION IN PROLAPSED CORDS	GROSS MORTALITY PER CENT	CORRECTED MORTALITY PER CENT
Vertex	95.3	61.5	30	25
Breech	4.1	26.0	38	34
Transverse	0.2	6.0	41	45
Face-brow	0.3	2.0	20	33
Compound	0.1	4.5	44	37

Cord Pulsations and Fetal Heart Rate Related to Infant Survival.—Table V indicates the fetal mortality rate for each possible combination of cord pulsation and fetal heart rate. As expected, the fetal mortality gradually increases from a low of 10 per cent in those cases where the fetus presents no evidence of anoxia prior to delivery to a high of over 90 per cent in cases where the fetal heart was not heard and cord pulsations were not felt.

TABLE V. FETAL HEART RATE AND UMBILICAL CORD PULSATIONS RELATED TO FETAL MORTALITY

UMBILICAL CORD PULSATIONS*	FETAL HEART RATE*	NO. OF CASES	FETAL MORTALITY PER CENT
1. Pulsating normally	Normal	96	10.5
2. Pulsating feebly or slowly	Normal	4	25.0
3. Pulsating feebly or slowly	Below 80 or above 160	23	34.7
4. No pulsation	Normal	3	33.3
5. No pulsation	Below 80 or above 160	10	60.0
6. No pulsation	Not heard	36	91.6

*Cord pulsation and fetal heart rate obtained just prior to attempted delivery.

A review of the fetal deaths occurring in the group which showed both normal cord pulsations and fetal heart tones prior to delivery reveals that they occurred mostly in the neonatal period. While the fetus was obviously uncompromised when the diagnosis was made, the actual delivery was usually preceded by time-consuming and difficult operative procedures which accounted for the deaths.

There were three infant survivals in cases where the fetal heart was not heard and cord pulsation not felt. All had easy, rapid delivery but were deeply shocked.

Methods of Delivery.—The methods of delivery are presented in Table VI, while Table VII shows trends in related obstetrical procedures.

Cord reposition was successful in 54 per cent of the cases with a fetal mortality of 48.6 per cent, which is above the total fetal mortality rate. Of note is the recent increase in the number of unsuccessful attempts to reposit the cord. The high fetal mortality associated with both manual dilatation of the cervix and use of the Voorhees bag is striking.

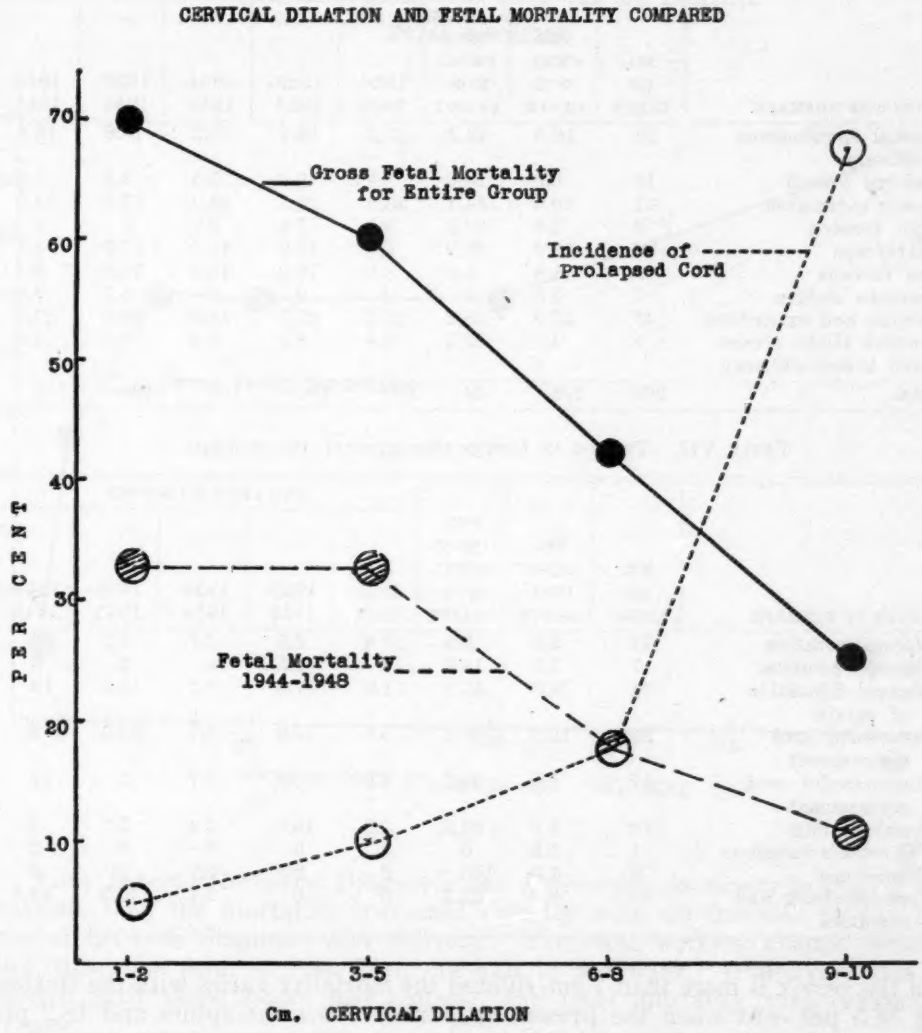

Fig. 3.

Of interest in the choice of methods of delivery and related operative procedures are the trends shown in each five-year period. Little change is in evidence for spontaneous delivery, mid and low forceps delivery, breech extraction, and version and extraction. There has been a decline in the use of high forceps, the Braxton Hicks version, and bagging procedures. The Trendelenburg position with elevation of the fetal presenting part has been used more frequently in recent years. This also is true of the cesarean section operation for this condition.

Station, Cervix, and Method of Delivery Related to Fetal Mortality.—The relationship of cervical dilation and station of presenting part at time of prolapse to fetal mortality is shown in Table VIII. Briefly, it may be summarized by stating that, when the cervix is unfavorable or less than 7 cm. dilated, the fetal mortality remains high, irrespective of the station of the presenting part.

TABLE VI. METHODS OF DELIVERY

TYPE OF THERAPY	NO. OF CASES	PER CENT INCIDENCE	PER CENT FETAL MORTALITY	PER CENT INCIDENCE				
				1924-1928	1929-1933	1934-1938	1939-1943	1944-1948
Normal spontaneous delivery	32	16.0	43.7	23.5	10.2	16.2	15.5	15.6
Assisted breech	10	5.0	20.0	2.9	7.6	5.4	2.5	5.9
Breech extraction	41	20.5	34.1	20.6	20.5	18.9	17.9	23.5
High forceps	6	3.0	83.3	5.8	7.6	2.7	0	0
Midforceps	26	13.0	26.9	8.8	10.2	16.2	17.9	11.7
Low forceps	23	11.5	8.6	8.8	12.8	16.2	10.2	9.8
Cesarean section	7	3.5	0	0	0	0	5.2	9.8
Version and extraction	47	23.5	38.2	23.5	25.7	18.9	28.2	21.5
Braxton Hicks version and breech delivery	8	4.0	62.5	5.8	5.2	5.4	2.5	1.9
Total	200	100	34	100	100	100	100	100

TABLE VII. TRENDS IN OTHER OBSTETRICAL PROCEDURES

TYPE OF THERAPY	NO. OF CASES	PER CENT INCIDENCE	PER CENT FETAL MORTALITY	PER CENT INCIDENCE				
				1924-1928	1929-1933	1934-1938	1939-1943	1944-1948
Manual rotation	11	5.5	9.0	10.4	2.5	2.7	7.5	4
Forceps rotation	7	3.5	14.2	0	2.5	0	5	8
Manual dilatation of cervix	24	12.0	45.8	11.6	17.5	8.1	12.5	10
Successful cord replacement	20	10.0	35.0	5.8	15.0	8.1	12.5	8
Unsuccessful cord replacement	17	8.5	64.7	5.8	10.0	2.7	5	12
Voorhees bag	10	5.0	60.0	5.8	10.0	5.4	5	0
Dührssen's incisions	1	0.5	0	0	0	0	0	2
Craniotomy	2	1.0	100	0	2.5	2.7	0	0
Trendelenburg and elevation	18	9.0	22.2	0	0	2.7	15.3	21.5

When the cervix is more than 7 cm. dilated the mortality varies with the station, being 36.5 per cent when the presenting part is above the spines and 18.2 per cent when below the spines. Obviously, then, the dilatation of the cervix is of more prognostic significance than is the level of the presenting part.

TABLE VIII. CERVIX AND STATION RELATED TO FETAL MORTALITY

CASES	CERVIX	MORTALITY PER CENT	GROSS FETAL MORTALITY PER CENT
93	8-10 cm.	+1-+5	18.2
52	8-10 cm.	-5-0	36.5
14	1- 7 cm.	+1-+5	57.1
41	1- 7 cm.	-5-0	58.7

When the various combinations of cervical dilatation and station of the presenting part were related to methods of delivery, no significant advantage for any particular method was noted. The mortality rate was related to cervical dilatation and station rather than to method of delivery. The only exception to this is noted in the group having an unfavorable cervix and an unengaged presenting part, in which the cesarean section has an obvious advantage over all other methods. Six cesarean sections were done in this group with no fetal loss.

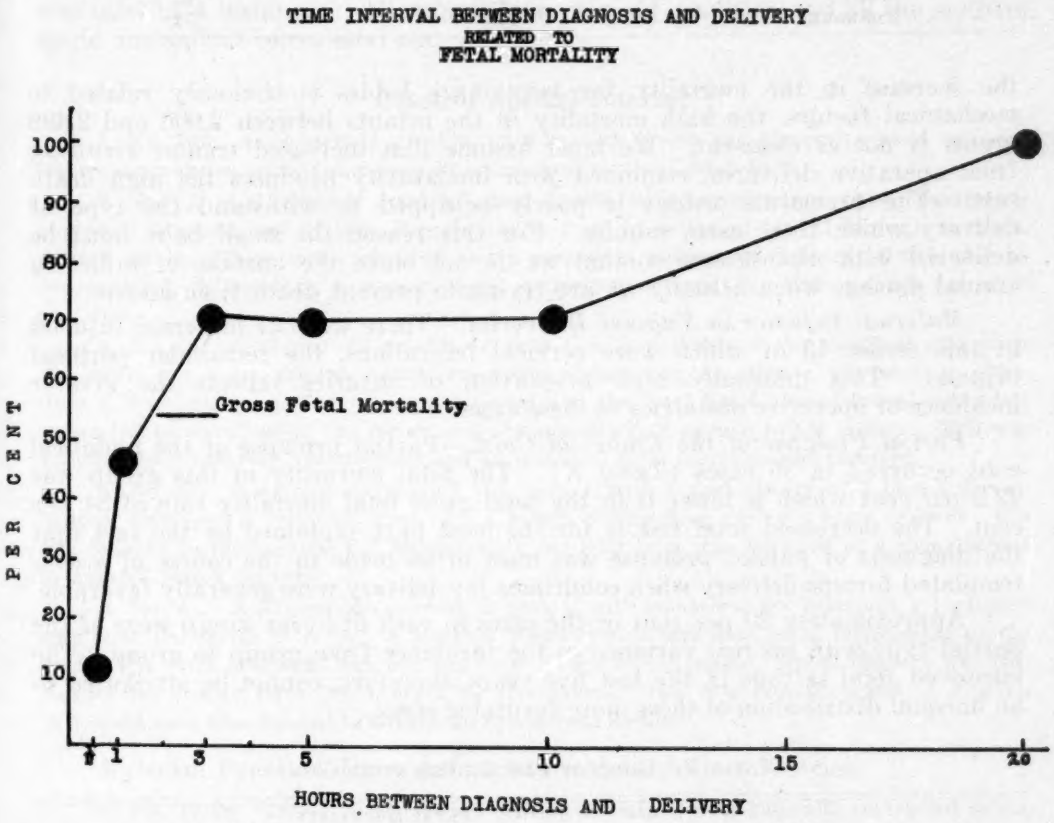

Fig. 4.

Time Interval Between Diagnosis and Delivery.—As shown in Fig. 4, it is apparent that the mortality increased directly with an increase in the time interval between diagnosis and delivery. The most striking change occurred when this time interval rose from one-half to one hour. If delivery was not effected until three hours had elapsed, the fetal mortality rate reached 70 per cent.

Time Interval Between Rupture of Membranes and Diagnosis.—There was some slight tendency for the fetal mortality to vary with the length of the interval between rupture of the membranes and the diagnosis of cord prolapse. Only when this interval was less than one hour was the fetal mortality below 34 per cent, the over-all gross average.

A comparison of this interval in each of the five-year groups reveals that the diagnosis has not been made earlier in recent years.

Infant Weight.—There was an increased fetal mortality rate in the infants between 2,000 to 2,500 grams and in those over 4,500 grams (Table IX). While

TABLE IX. INFANT WEIGHT

WEIGHT IN GRAMS	INCIDENCE PER CENT	GROSS FETAL MORTALITY PER CENT
2000-2499	9.0	50
2500-2999	24.0	29
3000-3499	27.5	29
3500-3999	15.5	29
4000-4499	9.0	22
4500+	2.5	40
Unknown	11.0	54

the increase in the mortality for very large babies is obviously related to mechanical factors, the high mortality in the infants between 2,000 and 2,499 grams is not as clear-cut. We must assume that increased trauma resulting from operative deliveries combined with immaturity produces the high death rate. The premature infant is poorly equipped to withstand the type of delivery which these cases require. For this reason the small baby must be delivered with utmost care so that we do not make the mistake of inflicting cranial damage when actually we are trying to prevent death from anoxia.

Maternal Injuries in Vaginal Deliveries.—There were 27 maternal injuries in this series, 13 of which were cervical lacerations, the remainder perineal injuries. This unusually high proportion of injuries reflects the greater incidence of operative obstetrics in these cases.

Partial Prolapse of the Umbilical Cord.—Partial prolapse of the umbilical cord occurred in 36 cases (Table X). The fetal mortality in this group was 22.2 per cent which is lower than the total gross fetal mortality rate of 34 per cent. The decreased fetal risk is for the most part explained by the fact that the diagnosis of partial prolapse was most often made in the course of a contemplated forceps delivery when conditions for delivery were generally favorable.

Approximately 20 per cent of the cases in each five-year group were of the partial type with no real variance in the incidence from group to group. The improved fetal salvage in the last five years, therefore, cannot be attributed to an unequal distribution of these more favorable cases.

TABLE X. CASES OF PARTIAL PROLAPSED CORD

GROUP OR YEAR	NO. OF CASES	FETAL MORTALITY PER CENT PARTIAL PROLAPSE	TOTAL GROSS FETAL MORTALITY PER CENT
1924-1928	6	33.3	44.0
1929-1933	5	20.0	48.9
1934-1938	11	27.2	29.1
1939-1943	5	20.0	35.8
1944-1948	9	11.1	15.6
Total	36	22.2	34.0

Prolapsed Cord Occurring Before Admission to the Hospital.—Sixteen additional cases occurred in which the prolapse took place at home and the patient presented herself subsequently for admission. The average duration between rupture of the membranes and admission to the hospital was approximately three to five hours. Two patients appeared within one-half hour and in one of these cases a living infant was obtained. The resulting fetal mortality was 87.5 per cent.

These patients are presented separately and are not included in the group tabulations because the infants were largely not salvageable.

Cesarean Sections.—Seven cesarean sections, 2 combined with hysterectomy, were performed in this series. The cervix varied between 3 and 7 cm. dilated and the station from –1 to –5. Operation was performed in all cases at approximately one hour or less after the diagnosis was made. In 3 cases the fetal heart rate was abnormal at one time or another. Likewise, the cord pulsations were abnormal in 3 cases. A combination of elevation of the presenting part while oxygen was administered to the mother placed in the Trendelenburg position was used in 4 instances. All infants were in good condition and all the mothers made uneventful convalescences.

Cases of Special Interest

1. No. 167. A 24-year-old gravida, para iv, with breech and transverse lie in two successive pregnancies, each terminating with prolapsed cord and fetal death.

2. No. 77. A 31-year-old gravida i, para 0, with multiple pregnancy. After membranes ruptured, foot and cord of twin B prolapsed in front of vertex of twin A through an 8 cm. dilated cervix. These were reposited and a successful midforceps delivery of twin A was accomplished, followed by a version-breech extraction of twin B. Both infants are alive and well.

3. No. 70. A 27-year-old gravida iv, para i, with prolapse of the umbilical cord when the cervix was 6 cm. dilated. After successful replacement, an attempt was made to introduce a Voorhees bag. The bag was expelled and the fetal heart slowed considerably but responded to elevation of the vertex and administration of oxygen to the mother. This was followed by a cesarean hysterectomy and an infant in good condition was obtained.

4. No. 61. A 44-year-old gravida viii, para v, with a past history of 3 breech presentations, developed a prolapsed cord with a breech presentation during a home delivery. She was brought to the hospital and aproximately one hour later was delivered of a living infant by assisted breech delivery.

5. No. 48. A 31-year-old gravida ii, para i, with transverse lie, sustained a prolapsed cord with the cervix at 6 cm. A Braxton Hicks version was done after replacement of the cord. The fetal heartbeat was lost one hour later and an assisted breech delivery was performed for a dead fetus two hours after the version. This case represents one of a group that could have been treated to advantage by cesarean section.

Maternal Deaths.—There were 4 maternal deaths in this series.

1. No. 11706. 1927. A 22-year-old gravida ii, para i, with generally contracted pelvis. Vertex presented at station -5 and, with the cervix at 9 cm. dilatation, the diagnosis of complete placenta previa was made. Version and extraction were done during which the cord prolapsed and a dead fetus was delivered. Profuse hemorrhage followed and despite supportive therapy the patient died after three hours. Postmortem examination revealed a tear of the lower uterine segment.

2. No. 441655. 1935. A 33-year-old gravida ii, para i, with android pelvis and twin pregnancy. A Voorhees bag was introduced because of cervical dystocia after twelve hours of labor. Twelve hours after insertion of the bag, the vertex of twin A reached the spines with the cervix at 8 cm. dilated. An easy forceps delivery was accomplished. The pulseless cord of twin B was found prolapsed. The fetal heartbeat was absent and thick meconium noted. Version and extraction were performed and a dead fetus was delivered. Hemorrhage and shock ensued due to a tear of the lower uterine segment. The patient died shortly thereafter before surgical procedures could be instituted.

3. No. 510093. 1937. A 30-year-old gravida v, para iii, with previous history of radium therapy for menorrnagia at another hospital. With the breech presenting at station -4, the cord prolapsed through an 8 cm. dilated cervix. The cord was not pulsating and the fetal heart was not heard. Manual dilatation of the cervix was followed by breech extraction of a stillborn fetus eight hours later. Profuse vaginal bleeding followed and after manual

removal of the placenta examination revealed a laceration of the cervix and another tear involving the vagina and cervix with extension to the broad ligament. Despite therapy, the patient died 45 minutes later.

4. No. 532243. 1941. A 32-year-old gravida ii, para i, with gynecoid pelvis and known rectal stricture associated with lymphogranuloma inguinale. With breech presenting, the cord prolapsed when the cervix was 3 cm. dilated. The fetal heartbeat did not change and, after the cord was manually replaced, a Voorhees bag was inserted. One hour later the fetal heartbeat was lost and twelve hours following this, an assisted breech delivery of a dead fetus was performed. Post partum the temperature rose to 106.0° F. and the patient became distended. She died after twenty-two hours. Autopsy revealed a rupture of a lymphogranulomatous rectal stricture with peritonitis.

Comment

This paper is concerned, for the most part, with fetal mortality as the common denominator in assessing the management of prolapse of the umbilical cord. Analysis of five-year fetal mortality rates has shown marked improvement in recent years. Although this may be partially explained by the fact that a greater percentage of the more recent cases occurred when the cervix was favorable for delivery, it can be pointed out that fetal salvage has been higher in this recent group even when comparable degrees of cervical dilatation are considered.

Fig. 5.

When the cervix is less than 7 cm. dilated and the infant is not compromised, cesarean section seems to be the safest method of delivery, providing, of course, that it can be done within a reasonable period of time. When the fetus has shown evidence of distress, we have had better results if the presenting part is elevated with the patient anesthetized before any type of delivery is attempted. Anesthesia favors this displacement and limits further compression due to uterine contractions. On a theoretical basis at least, cyclopropane is

best suited for two reasons, speed of induction and because it permits a relatively greater amount of oxygen to be delivered to the fetus. We believe that the use of these procedures in the 1943-1948 group has contributed to improved fetal salvage.

From the data it appears evident that cord reposition, Braxton Hicks version, and the use of the Voorhees bag are poor substitutes for cesarean section when the latter is feasible. The improved recent fetal salvage can actually be accounted for by the fact that these vaginal procedures have been largely abandoned.

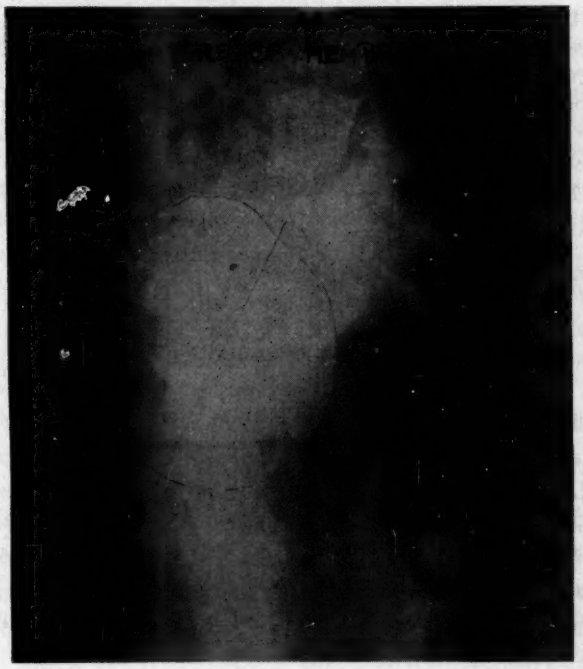

Fig. 6.

The high fetal mortality in the group of cases presenting a favorable cervix with the presenting part above the spines needs comment. The salvage was only one-half that of the group with the same cervical dilation with the presenting part below the spines. Analysis of the infant deaths in the former group reveals that with the cervix favorable for delivery, speed of extraction of the infant was the dominant consideration in management. This haste to accomplish the delivery seemed to take precedence over any preliminary procedure which would permit the fetus to re-establish its already embarrassed circulation. In spite of the attempt to hasten the delivery from the high station, it was more often time-consuming and shocking to the already compromised infant. A badly shocked baby was often the result, with subsequent death in the neonatal period a common occurrence. In retrospect, it would seem wiser to allow the infant to re-establish his circulation as much as possible by such procedures as the Trendelenburg position, anesthesia, and manual displacement of the presenting part prior to operative delivery. Improved methods of infant resuscitation should also help to raise the fetal salvage in this group.

We reiterate, in this discussion of therapy, suggestions made by other writers on the subject. Abnormal presentation and multiple pregnancy are associated with this complication so frequently that in such patients we should anticipate its occurrence. Routine procedures, such as careful and frequent

auscultation of the fetal heart and periodic rectal examinations, cannot be overemphasized. We believe that a pelvic examination should be made after rupture of the membranes whenever the presentation is abnormal, or the presenting part is above the brim, or the pregnancy is of the multiple variety.

In previous years, the patient in early labor with ruptured membranes and a high presenting part has been kept in the prone position because it was commonly believed that the upright position in these patients predisposed to prolapse of the umbilical cord. However, in this series, with very few exceptions, the prolapse occurred while the patient was in a recumbent position. X-ray lateral views in the standing and recumbent positions were taken of a patient whose membranes had ruptured in early labor while the head was still unengaged. These are shown in Figs. 5 and 6. It is evident from these films that, in the standing position, more of the presenting part dips below the pelvic inlet, theoretically leaving less room for the cord to prolapse. It is our contention that a more rational treatment of these cases with ruptured membranes and a high presenting part is to allow the patient out of bed and to encourage ambulation. Cases of transverse lie and true cephalopelvic disproportion should be excepted.

When the station of the presenting part is unengaged, the membranes intact, and the cervix 7 cm. or more dilated, there is definite risk of prolapse of the cord with sudden rupture of the amniotic sac. As a prophylactic measure in these cases, a few have been managed successfully by slow decompression of the sac with a long No. 18 needle. This method may have considerable merit in this small but potentially hazardous group of cases and deserves further exploration.

Summary

1. Two hundred sixteen cases of prolapse of the umbilical cord occurring over a twenty-five-year period at Sloane Hospital for Women have been reviewed.

2. The over-all fetal mortality was 34 per cent.

3. Five-year trends have been analyzed and recent improvements in fetal mortality have been noted.

4. Some methods of treatment have been suggested relating to condition and station of the infant and dilatation of the cervix.

References

1. Anderodias, J., Mahon, R., and Dagorn: Bull. Soc. d'obst. et de gynéc. 22: 537, 1933.
2. Gusberg, S.: Am. J. Obst. & Gynec. 52: 826, 1946.
3. Cragin, E. B.: The Practice of Obstetrics, Philadelphia, 1916, Lea & Febiger.
4. Kurzrock, J.: Am. J. Obst. & Gynec. 23: 403, 1932.
5. Bourgeois, G. A.: Am. J. Obst. & Gynec. 41: 837, 1941.
6. Stander, H. J.: Williams Obstetrics, ed. 7, New York, 1936, D. Appleton-Century Company, Inc.
7. Beck, A. C.: Obstetrical Practice, ed. 3, Baltimore, 1942, The Williams and Wilkins Company.
8. Mengert, W. F., and Longwell, F. H.: Am. J. Obst. & Gynec. 40: 79, 1940.
9. Schiller, W.: Monatschr. f. Geburtsh. u. Gynäk. 88: 52, 1931.

THE LATE COMPLICATIONS FOLLOWING IRRADIATION OF PELVIC VISCERA*

WILLIAM CRAWFORD WHITE, M.D., F.A.C.S., AND
FREDERICK WALL FINN, M.D., F.A.C.S.,
NEW YORK, N. Y.

(From the Woman's and the Roosevelt Hospitals)

THE subject of this paper constitutes a common meeting ground for many surgical specialities. The complications are due to radium and roentgen therapy for carcinoma of the uterus and occur months to many years after treatment. The relationship of the late manifestations may not be obvious unless the surgeon is aware of the possibility. Furthermore, he must not jump to the conclusion that these symptoms are due to recurrence of the carcinoma.

In this paper it is not pertinent to go into the history of the development of radium and roentgen therapy for carcinoma of the uterus. It is perhaps sufficient to state that some of the damage, of which we shall speak, has been due to overdosage, either too much at once, or too much in too short a time.

We shall not try to settle the dispute as to whether the radium or the roentgen ray is the malefactor. Corscaden, Kasabach, and Lenz,[1] in order to attempt to reduce their complications, reduced their initial dose of radium. They gave it over a longer time, with favorable reduction in complications, although the roentgen-ray technique remained the same. This seemed to indicate that radium therapy is the chief offender. Also, it is to be noted that the overwhelming incidence of complications, in our records, is related to the treatment of carcinoma of the cervix and not to the treatment of carcinoma of the corpus.

Cancer of the cervix is a lethal disease. Adequate doses of radium and roentgen ray will be necessary, if cure is to be the goal. Screening off the surrounding tissue is always inadequate, so that some of these complications will inevitably develop. In a real sense this paper is a compliment to this form of therapy, for we are discussing late complications, which in the majority of cases occur in patients who are free of further evidence of cancer.

Experience in the past few years seems to indicate that we may be able to reduce the incidence of injuries to the urinary tract and the bowel by routine treatment of the cervical neoplasm with antibiotics and roentgen therapy, before the application of radium.

In this paper we shall discuss late damage to bones, urinary tract, and the intestines.

Bone Injuries

In 1926 Ewing[2] described the pathology produced in bone as a result of irradiation. He felt that the system of lacunae and the vascular channels were easily obstructed in the Haversian and Volkmann's canals. The end result was

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to produce osteoporosis secondary to vascular absorption and osteoplastic activity. This produces brittle bones, more subject to fracture.

In our own records we have been able to discover only one clear-cut case of spontaneous fracture following pelvic irradiation. However, it has been fully described in the literature. First mention was made by Baensch[3] in 1927, who described a patient who suffered a bilateral spontaneous fracture of the neck of the femur after x-ray and radium treatment for cancer of the cervix. In the next 10 years about 10 more cases were described by different investigators. In 1936, Dalby, Jacox, and Miller,[4] of the University of Michigan, presented 14 cases of spontaneous fractures of the necks of the femur. This injury we now know is the most common fracture resulting from irradiation. An occasional fracture of the pubis has been described, but it is by far in the minority. In the cases presented by Dalby, Jacox, and Miller,[4] it is of interest to note that the lateral ports had not been used. Also, almost all fractures were preceded by prodromal period of pain in the hip. This warning pain was also described by C. H. Heyman,[5] who reported a case in 1945. This patient developed pain first in one hip and then in the other, 14 and 18 months after her radiation therapy. Approximately 4 weeks after the onset of pain, spontaneous fractures of the neck of the femur were shown roentgenographically. Both hips were relieved of pain by insertion of a Smith-Petersen nail. In both a bony union was obtained.

In 1947, Stampfli and Kerr[6] of the University of Iowa reported spontaneous fractures in 12 patients out of 1372 who had received intensive pelvic irradiation. From this and other figures we believe the incidence of fractures to be only about 1 per cent. They divided their cases into three groups. In the first, which was composed of incomplete fractures, healing was obtained by bed rest alone. Their second group consisted of those patients who had fractures with little displacement. Some were treated conservatively and some with internal fixation. In the third group, i.e., fracture with gross displacement, they used various procedures, such as internal fixation, subtrochanteric osteotomy, and reduction and immobilization. The results in this last group were considered satisfactory, in view of the type of fracture.

Another surgical treatment has been reported by Phemister,[5] namely, the use of internal fixation with free onlay grafts taken from the tibia.

Urinary Tract Injuries

It has been known for years that there are urological complications following irradiation therapy to the pelvis. It is common knowledge that cystitis occurs immediately, in most cases. But it is not so commonly recognized that late complications occur. This is partly due to the separation of urology and gynecology in most clinics, so that often the urologist sees these cases, and his findings do not appear on the original records. Also, since these complications may appear years later, the patient may, by this time, be under the care of some other physician. In brief, our records are inadequate as to the percentage, although we have examples of most complications.

Everett[7] first reported on this subject in 1934, and since then has been keenly interested in the problem. In 1949, he[8] reported that their complications have been: (1) indolent ulcers of the bladder, (2) vesicovaginal fistula, (3) intramural stricture of the ureter, (4) with secondary hydrouretero nephrosis. Dean,[9] in 1933, gave a similar report.

It has been our custom to cytoscope every patient, and also make an intravenous pyelogram before starting irradiation therapy. This has the advantage of determining whether or not a urological disease is present. Also, the films are available for later references.

The late complications may come on suddenly in a patient who was believed to be in good health. Her symptoms are frequency, hematuria, and dysuria. Examination with a cystoscope may show localized edema surrounding an indolent ulcer covered with gray slough. Rarely is surgery necessary, as under palliative treatment, the ulcer usually clears up. If not, a vesicovaginal fistula may develop, which may require some difficult surgery.

Fig. 1.—B. H. (43431), a 47-year-old white woman, was treated in 1935 with radium and roentgen therapy for squamous carcinoma of the cervix. In 1947 roentgen examination showed a stricture of the intramural portion of the right ureter. An attempt to transplant the ureter into the bladder wall was unsuccessful. In 1948 the right kidney had to be removed. The patient is alive and well 15 years after original treatment.

There is another group in which the onset is more insidious. The bladder symptoms are less marked, but in addition the patient may have pain in the flank or upper quadrant, with chills and fever. Investigation reveals a stricture of the ureter, with dilatation above and hydro- or pyonephrosis. If this is recognized early enough, the kidney may be saved, and the patient relieved by dilatation of the stricture. If such a procedure is of no avail, the kidney and the ureter may have to be sacrificed.

In summary, we desire to urge the necessity of urological study before irradiation treatment and frequently afterward. The early detection of damage to the urinary tract may thus permit early treatment, before severe damage has

occurred. All too often these patients have had diagnoses of lethal recurrence, when a proper urological study would not only have disproved this diagnosis, but also pointed to a remedy.

Fig. 2.—E. S. (33713, R. H.), a 58-year-old woman received radium and roentgen therapy in 1945 for carcinoma of the cervix. In 1947 she was treated for chronic cystitis. In 1949 a moderate bilateral hydronephrosis was found and was treated by dilatation of the bilateral ureteral strictures. This film was taken in February, 1950, and shows progression of the right hydroureteronephrosis. The right kidney was removed. The patient is being treated for a less severe stricture of the other ureter.

Intestinal Injury

The percentage incidence of this complication is difficult to determine, because many of the milder complications are not seen or else not recorded in the histories. Second, the late complications are often seen in distant clinics. As nearly as he can estimate, Aldridge,[10] of the Woman's Hospital, believes, that "about 17 per cent, or approximately one in six patients treated, had a post-irradiation intestinal stricture." Maas,[11] of Wisconsin General Hospital, reports that 50 to 75 per cent of their patients bear permanent rectal residual changes.

It is well known that proctitis frequently develops early in the course of treatment. There are likely to be nausea, abdominal cramps, tenesmus, diarrhea, and often bloody stools with mucus. Proctoscopy will reveal edema and vascular congestion of the mucous membrane, especially opposite the level of the

cervix. Usually this is of moderate degree and clears up gradually under palliative therapy. If not, there is continuing deterioration as a result of thrombosis of the small blood vessels, with resulting ischemia and ulceration of the mucous membrane. Erosion into a large blood vessel may occur with severe or fatal massive hemorrhage. A process of repair eventually goes on, even if, in the interval, a rectovaginal fecal fistula has developed. If this rectal area is inspected later on with a proctoscope, a thin pale mucous membrane with scar tissue formation and areas of telangiectasis will be noted. It is well to comment, at this point, that even small doses of radium may cause damage, due to special sensitivity of intestinal mucous membrane.

Fig. 3.—M. T. (70965), aged 63 years. Squamous carcinoma of cervix. December, 1939, radium followed by roentgen therapy. April, 1940, definite signs of large bowel obstruction. Operation, April 27, 1940. Sigmoid colon had rubber-tube induration 10 cm. long. Serosa had pearl-gray color with telangiectasis. Colostomy only because of extensive cancer invasion of vagina. Died, July, 1940.

We have not had a long enough time to observe the benefits of intestinal antibiotics. It is fair to believe that this new aid will prove of great benefit, especially when ulcers appear with their inevitable secondary infection.

There is good reason to believe that the pathological process seen in the rectum also occurs in the colon beyond the reach of the proctoscope. Probably the response is less acute and more gradual, because the intestinal complications about which we are speaking, usually are first noticed about six months after the initial treatment. This is due to a slow pathological change, caused by the action of the radium and roentgen ray on the intestines. There is a thrombosis of the blood vessels, with diminished blood supply and eventual necrosis of the mucous membrane. At this time the patient has the physical signs of colon irritation, but with little barium x-ray evidence of more than spasm. In many of these cases, this is the maximum destruction that occurs. The ulcer heals with a minimum of scar contracture, so that there is little evidence of interference with the bowel movement.

In other cases the pathological changes go on to a cordlike stricture. As a result the patient has obstructive symptoms, mild to severe, at times requiring emergency operation. More commonly, a more extensive pathological change develops. The bowel on examination has the feel of a rubber hose, the serosa has a pearl-gray color with numerous telangiectases to be seen on its surface. On section, the wall has increased in thickness, due to fibrosis, the mucous membrane has atrophied, while indolent ulcers covered with gray slough may be seen. The caliber of the lumen has been reduced to pencil size or less, so that not only is the patient suffering from irritated bowel, she also has partial to complete obstruction.

As is to be expected, the major intestinal injury is to the rectum, rectosigmoid, and sigmoid. It is difficult to see how this can be avoided, for there is no effective way of completely screening off this bowel.

Fig. 4.—E. L. (55947), aged 45 years. Squamous carcinoma of cervix. Radium treatment of cervix, November, 1933, and March, 1934. Abdominal symptoms began in 1939. In March, 1940, this picture was taken. The sigmoid was involved 10 cm., with a contracture at one point and lumen 1 cm. in diameter. Resection and end-to-end anastomosis. Died in January, 1942, of carcinoma.

When symptoms of obstruction arise and barium enema shows a point of narrowing of the sigmoid, what should be done? Is it a sign of recurrence? Has the patient arrived at a hopeless terminal state? Todd[12] tells us that he first felt this way, and so was content to do palliative colostomy. Finally it dawned on him that this condition was due to irradiation and not to cancer. The proof was that the patients lived on and on. More and more, we have become aware that this set of symptoms is related to radiation injury and not to cancer recurrence. If so, we must adopt a different approach.

McIntosh and Hutton[13] are impressed with their success in palliative treatment. They feel that too much surgery has been done. As argument, they show x-ray evidence of sigmoid stricture of marked degree, with the patient comparatively comfortable. We have followed their work in the clinic at The

Woman's Hospital, and are assured that many have done amazingly well, in spite of bizarre barium x-ray picture. In the final analysis it comes down, not only to the x-ray findings, but also to the physical symptoms and the pathology. It must always be borne in mind that this process usually is a continuing one. For this reason, we believe, that they are too conservative. Of our 26 patients who were given palliative treatment only, we know that, to date, two died of massive intestinal hemorrhage and two died from intestinal perforation with general peritonitis.

When there is ulceration through the bowel wall into the peritoneal cavity, we have symptoms that are not unlike those of acute diverticulitis with perforation. Prompt incision and drainage are indicated. More surgery may be necessary, if there is the usual coincident obstruction.

Fig. 5.—R. W. (74210), aged 40 years. Squamous carcinoma of cervix. Radium and roentgen therapy, February and March, 1941. Abdominal symptoms began soon afterward. In October, 1941, we had the above picture. At operation there was almost complete obstruction at the rectosigmoid. Abdominal-perineal resection. October, 1950, in good health.

Many of these patients are miserable with symptoms of partial obstruction of the colon. Ten years ago, it was considered correct routinely to do a permanent colostomy only. A Mikulicz-Paul type or obstructive resection type of colostomy is rarely feasible, as the involved bowel is usually too distal and too fixed. Since the advent of the antibiotics, and more thorough preoperative colon preparation, it has become possible to do a wide excision, with open end-to-end anastomosis. An enema tube is passed through the rectum and the anastomosis for use as a gas vent. This avoids the need of the preliminary cecostomy or transverse colostomy, as had previously been advocated in primary resection, with immediate end-to-end anastomosis, by White and Amendola.[14]

There is still a place for sigmoid colostomy, temporary or permanent. For example, we have had one patient with irradiation ulcers of the rectosigmoid who received temporary colostomy. At the end of one year, the mucous membrane had healed and there was sufficient diameter of lumen so that we were

able to close the colostomy. This opportunity is but rare; all our other colostomies have been permanent.

The primary resection is preferable. It is not to be used if there is any question of insufficient blood supply. It is to be remembered that damage to blood vessels is one of the primary irradiation injuries. If resection is not possible, then a colostomy is necessary.

While injuries to the large bowel are more common, the strictures of the ileum are frequent enough to make one suspect this in cases of partial intestinal obstruction, six months to many years after irradiation. Small bowel studies with x-ray may be of some help. Often it must be a clinical diagnosis of intestinal obstruction. The usual site of the lesion is in the lower end of the ileum.

Our first experience with injury to the small intestine was in a "cervical stump" case. The patient previously had had a supravaginal hysterectomy. Years later she developed carcinoma of the cervix, for which radium and roentgen-ray therapy was given. She was first seen by us seven months later with acute small-bowel obstruction. Subsequently, at operation, it was demonstrated that a loop of ileum was adherent to the pelvic side of the stump, so that it had received the full force of the radium. As a result of similar experience with other stump cases, we believe that at least x-ray intestinal studies should be made before radium is applied, to see if there is evidence of a fixed loop of small bowel in the pelvis, lying against the pelvic side of the stump. We believe that even an exploratory celiotomy to investigate may be justified.

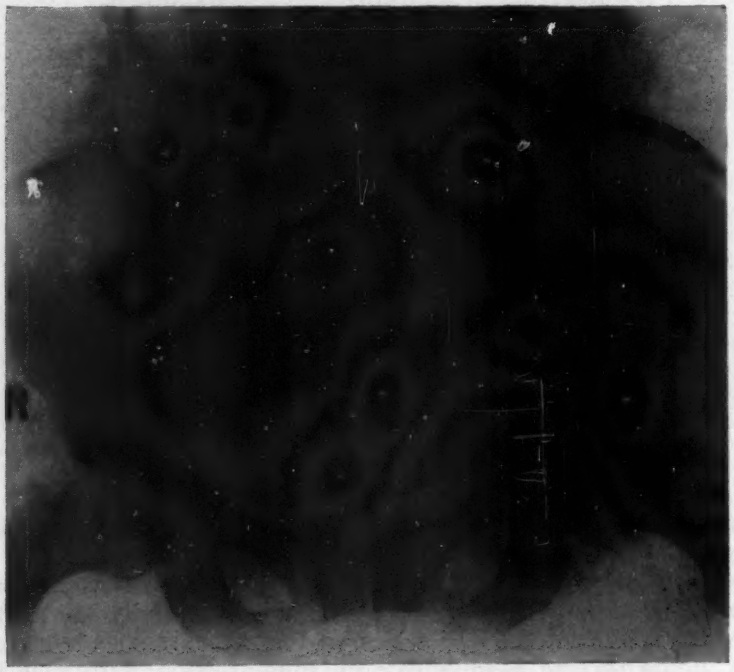

Fig. 6.—M. G. (9571), aged 60 years. Carcinoma of fundus. March, 1941, radium in uterus. May, 1941, complete hysterectomy. July, 1941, ileovaginal fecal fistula. July 18, 1941, resection of ileum. October, 1950, in good health.

We feel that in most cases of injury to the ileum, it has been due to the proximity of the bowel to the uterine organs as a result of adhesions. But there are cases in which the ileum has been injured where there never has been any evidence, at operation, of adhesions to the pelvis.

One must also be aware of the possibility of coincident irradiation injury to both sigmoid and ileum. We have had two such cases.

One was in a patient who had received her therapy fourteen years previously. We resected the sigmoid constriction, with partial benefit, only to be forced four months later to reoperate for a double lesion of the ileum, because of continuing symptoms of partial small-bowel obstruction.

In the operative mortality of seven, six had coincident obstruction and abscess. One had massive intestinal hemorrhage one month after operation.

From a study of our cases of intestinal damage, a list of which is given in Table I, we believe that certain cases may be treated conservatively. However, this is not without risk. It is necessary to follow these patients closely, as the disease may progress and go on to complete obstruction, perforation, or fatal hemorrhage. Our high operative mortality was largely due to the fact that operation had been unduly delayed in many patients, who were being treated too conservatively. It is to be noted that often emergency treatment was necessary, and also that necrosis of the bowel with perforation and abscess had developed by the time they had come to operation. In fact, when abscess had occurred, there were no recoveries. In contrast to this, in those patients who were operated upon electively with adequate preparation we had no fatalities.

TABLE I. IRRADIATION INTESTINAL DAMAGE, 1938-1950

Number of cases	55
Palliative treatment	26 with 4 deaths, 2 died of massive hemorrhage, and 2 died of general peritonitis
Operative Treatment	29 with 7 deaths
A. Resection of ileum	10 with 3 deaths
B. Resection of ileum and colostomy	3 with 1 death
C. Primary resection of colon	4 with no death
D. Abdominal perineal resection	1 with no death
E. Colostomy	11 with 3 deaths

Summary and Conclusions

I. Bones.—

A. The bone most usually affected by the pelvic irradiation is the neck of the femur.

B. Spontaneous fracture occurs in about 1 per cent of cases so treated.

C. These fractures occur usually more than one year following the x-ray therapy and are often preceded by a warning pain in the hip.

D. Fractures without displacement will frequently heal with conservative therapy. Fractures with displacement are treated according to the usual orthopedic procedure.

II. Urinary Tract.—

A. Following irradiation therapy of the pelvis, damage to the urinary tract may not manifest itself for years.

B. The most common injuries result in indolent ulcers of the urinary bladder or strictures of the ureter resulting in secondary hydroureteronephrosis.

C. When urinary symptoms occur they should not be considered a sign of recurrence until adequate urological studies have been made.

D. These urological studies should have been made prior to the irradiation treatment and at regular intervals thereafter. This would enable the urologist to institute a course of treatment before severe irreparable damage is done.

III. Intestines.—

A. Following irradiation therapy there is often permanent damage to the rectum, the sigmoid colon, and the ileum.

B. The pathology consists of thrombosis of the vessels, necrosis of the mucous membrane with fibrosis of the wall of the intestines, and secondary contracture of the lumen.

C. The ulcerations may erode into large vessels which had not been thrombosed, resulting in massive hemorrhage; or they may erode through the wall, so as to produce a perforation with peritonitis.

D. In many cases the contracture is sufficient to produce partial or complete obstruction.

E. Our experience has shown that many may be treated in a conservative fashion, but that they must be under constant supervision, because the disease is progressive. Despite utmost care this course is not without risk.

F. Although conservative therapy is possible, in many cases elective surgery is preferable. Early selection of these cases would give less morbidity and less mortality.

References

1. Corscaden, J. A., Kasabach, H. H., and Lenz, M.: Am. J. Roentgenol. **39**: 871, 1938.
2. Ewing, J.: Am. J. Roentgenol. **15**: 93, 1926.
3. Baensch, W.: Knochenschadigung nach Roentgenbestrahlung, Fortschr. a. d. Geb. d. Röntgenstrahlen. **36**: 1245, 1927.
4. Dalby, R. G., Jacox, H. W., and Miller, N. F.: AM. J. OBST. & GYNEC. **32**: 50, 1936.
5. Heyman, Clarence H.: J. Bone & Joint Surg. **27**: 674, 1945.
6. Stampfli, W. P., and Kerr, H. D.: Am. J. Roentgenol. **57**: 71, 1947.
7. Everett, Houston S.: AM. J. OBST. & GYNEC. **28**: 1, 1934.
8. Everett, H. S., Brach, C. B., and Farber, G. J.: AM. J. OBST. & GYNEC. **58**: 908, 1949.
9. Dean, Archie L.: AM. J. OBST. & GYNEC. **25**: 667, 1933.
10. Aldridge, A. H.: AM. J. OBST. & GYNEC. **44**: 833, 1942.
11. Maas, J. M.: AM. J. OBST. & GYNEC. **56**: 249, 1948.
12. Todd, T. F.: Surg., Gynec. & Obst. **67**: 617, 1938.
13. McIntosh, H. C., and Hutton, J. E.: Am. J. Roentgenol. **52**: 647, 1944.
14. White, W. C., and Amendola, F. H.: Ann. Surg. **120**: 572, 1944.

107 EAST 85TH STREET

THE CLINICAL BEHAVIOR OF GRANULOSA-CELL TUMOR OF THE OVARY*

WILLARD G. FRENCH, M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, Methodist Hospital)

DURING the past twenty years a considerable amount of investigative work has been done in the field of the so-called "feminizing tumors" in general and in the group of granulosa-cell tumors in particular. In evaluating the mass of reports concerned it would seem worth while to those who are strictly clinicians to attempt to correlate our own clinical observations in handling such cases, to report unusual behavior syndromes, and to try to clarify and group symptoms and findings helpful in the day-by-day management of these problems. With such a thought in mind two cases of ruptured granulosa-cell tumor with extensive intra-abdominal hemorrhage were reported nearly two years ago.[1] A further study of our individual pathology reports at the Methodist Hospital in Brooklyn, N. Y., failed to reveal any similar instance. From Jan. 1, 1918, to Dec. 1, 1950, 49,586 general case specimens were examined. In this group only 4 cases of granulosa-cell tumor could be found in a period of almost thirty-two years. Fifty per cent of this meager series revealed a spontaneous rupture of the capsule with hemorrhage as noted above.

Case Reports

CASE 1 (June, 1938).—F. L., 39-year-old, white, gravida 0, para 0, complained of pain in the right lower abdominal quadrant of two years' duration, radiating to right groin and leg and appearing in intermittent attacks of about seven days' duration. For five months moderate premenstrual dysmenorrhea was noted with a shortening of the menstrual cycle from twenty-eight days to twenty-five days (regular three- to four-day flow), last menstrual period date was not stated. Appendectomy had been done at 18 years of age. Admission blood count revealed red cells 4,270,000, hemoglobin 76 per cent, white blood cells 9,950, polymorphonuclear leucocytes 68 per cent, lymphocytes 32 per cent, and sedimentation time over 120 minutes. Urine analysis was negative. Operation consisted of right salpingo-oophorectomy with cystectomy, lysis of omental and pelvic adhesions, left partial salpingectomy, and suspension of the uterus. Left ovary was normal. The uterus was normal in size and shape.

Report of tissue examination: *Gross.*—The tube and ovary were firmly adherent to each other. The tube was distorted. The ovary was twice normal size and contained minute cysts and corpora lutea. A spherical nodule 1.5 cm. in diameter was attached to the surface of the ovary. On section it was solid and somewhat soft and the cut surface was yellow and homogeneous. *Microscopic.*—Cross section of the tube revealed rather marked thickening of the stroma of the tubular folds and some infiltration of the stroma with small round cells. There was also moderate thickening of the muscular coat.

Section of the ovary showed the presence of several large cysts of follicle origin lined by a single layer of flattened epithelium. There was also an old corpus luteum cyst, the lumen of which was filled with organized blood clot. Many corpora albicantia were observed in the stroma.

*Presented, by invitation, at a meeting of the New York Obstetrical Society, Dec. 12, 1950.

Sections of the tumor showed groups and columns of epithelial cells supported by a scanty fibrous stroma. The cells were small and mostly polyhedral though a number were cuboidal in shape. The cytoplasm was clear or opaque and the nuclei were round and took a moderately deep stain. Most of the cell groups had no pattern but here and there were small follicles composed of cuboidal cells. The tumor was very vascular and contained many capillary blood vessels.

Diagnoses.—Granulosa-cell tumor of ovary; polycystic ovary, follicular type; chronic salpingitis.

The patient's postoperative course was uneventful. Menstruation did not occur during hospital stay but her normal cycle was resumed and so continued until 1946, an interval of eight years. At this time, patient began manifesting menopausal symptoms and periods became irregular. The last menstrual period was in May of 1948, the patient being 49 years of age. She was last seen June 16, 1950, at which time abdominal and pelvic findings were negative. Papanicolaou smear was postmenopausal in character and revealed little estrogen function.

Follow-up period of twelve years.

CASE 2 (August, 1942).—J. R., 42-year-old white housewife, gravida ii, para ii, complained of intermittent, progressive pain in the epigastrium radiating to the left of the umbilicus. Pain was of one month's duration and was aggravated by moving and epigastric pressure. She also complained of an increasing, insensitive, mobile mass in the left lower abdominal quadrant first noticed four to five weeks prior to hospital admission. She had sustained a ten-pound weight loss during the same interval. Menses had been irregular, occurring every six to ten weeks for "several years" and with a scanty two to two and one-half day flow. The patient had not menstruated in over four weeks prior to hospital admission. (The patient's history was described as not entirely reliable.)

On admission to hospital temperature was 99.8° F., pulse 86; blood pressure 110/70; hemoglobin was 10.3 Gm.; white cells 16,800; polymorphonuclear leucocytes 80 per cent; lymphocytes 20 per cent; urine negative; Wassermann negative; Friedman test negative. Barium enema revealed the lower portion of the descending colon to be displaced by a rounded mass the size of a grapefruit. A lead rubber catheter was seen within the right side of the abdomen. Intravenous pyelogram revealed the kidney shadows to be normal.

Operation consisted of left salpingo-oophorectomy and cystectomy and removal of a catheter. The catheter was found extending from the right cornual area of the uterus to about the level of the ensiform. It was enclosed in a distinct organized tract completely encased in omentum and adherent to the cecum and transverse colon. In the opinion of the operator, the catheter had been there "many months." The uterus and right adnexa were not described. The left adnexal mass was adherent to the uterus in the left cornual area.

Report of tissue examination: *Gross.*—The specimen was that of a tumor of the uterus, which had already been sectioned longitudinally. It was kidney shaped and within its concave border was a roughened area which was yellowish brown in color, apparently the site of attachment. In the same area there was a Fallopian tube which was of normal size and shape. The lumen was patent throughout, the mucosa seemed somewhat thickened and firm in consistency. The tumor growth was covered by a firm, grayish-white, fibrous capsule. There were numerous nodules protruding upon the surface of the capsule. One was the size of a peach pit and was cystic in appearance and consistency. When opened, it was filled with a clear, amber-colored fluid. On section the cyst was found to be multilobular in type and its inner wall was smooth and shiny. On section through the cystic area one encountered another cyst of smaller size which was filled with a soft, oily, greasy substance. The cut surface of the tumor was composed of yellow-colored tissue, which in some areas was firm in consistency, and in others was rather soft. *Microscopic.*—Tumor: One section showed part of the ovary containing a small cyst lined by lutein cells. The other sections showed an epithelial new growth. It was composed of branching groups

of epithelial cells in the fibrous stroma. In some areas the tumor cells predominated. In other areas the stroma was abundant and the tumor cells were of medium size and were polyhedral or columnar in shape. The cell outlines were indistinct and the cytoplasm was pink. The nuclei were of medium size and were round or oval and dusty. The tumor cells showed a tendency to form small rosettes or alveoli. In the former the epithelial cells were arranged in a sun-ray pattern with the nuclei at the periphery. These groups had no lumina. In the latter the cell groups had a small lumen and some contained a minute spherical mass of homogeneous pink-staining matter. One of these masses resembled an ovum. In a few areas the tumor cells were arranged in a microfolliculoid pattern.

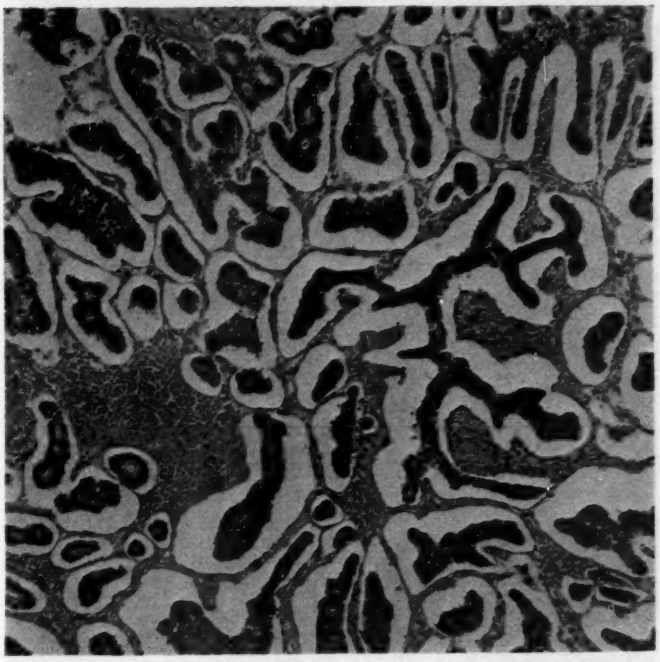

Fig. 1.—Photomicrograph of granulosa-cell tumor of Case 2. Trabecular microfolliculoid pattern. (Hematoxylin and eosin. ×100.)

Tube: Some of the villi were fused and some were enlarged and fibrotic. The muscularis was infiltrated with a small number of pus, round, and plasma cells.

Diagnosis.—Granulosa-cell tumor of ovary; chronic salpingitis.

The postoperative course was entirely uneventful. Menses were not resumed until four months following operation when patient flowed once for three days. There have been no menses since. Patient is at present living and well. She complains only of an occasional "hot flash." She is working regularly in addition to caring for her home. She married for the second time shortly after her operation and her husband has to date forbidden permission for examination.

Follow-up period of eight years (no examination).

Since the following two cases have been reported in detail elsewhere,[11] only a brief résumé and follow-up will be given.

Case 3 (November, 1946).—E. S., 32-year-old white, Jewish housewife, gravida ii, para i, with a history of seven hours of progressive right lower abdominal pain and a tumor of the right ovary known for ten weeks; three and one-half years of sterility and three years of irregular menses occurring every five to twelve weeks, last two periods prolonged to fourteen and ten days; last menstrual period forty-three days prior to admission.

The patient went into severe shock on being moved from her bed to a stretcher. She was taken immediately to the operating room, transfused, and a right salpingo-oophorectomy and cystectomy done. The tumor was not twisted and revealed a 7 cm. tear in its capsule. An amount estimated at 1,500 c.c. of fresh blood was found in the abdominal cavity. The uterus was slightly enlarged; left adnexa negative.

Pathologic Diagnosis.—Granulosa-cell tumor of right ovary with rupture and hemorrhage.

The postoperative course was uneventful. Menses appeared on the third day following surgery and thereafter resumed a normal thirty-day cycle with five days' flow. Seventeen months following operation, the patient delivered uneventfully a thirty-nine

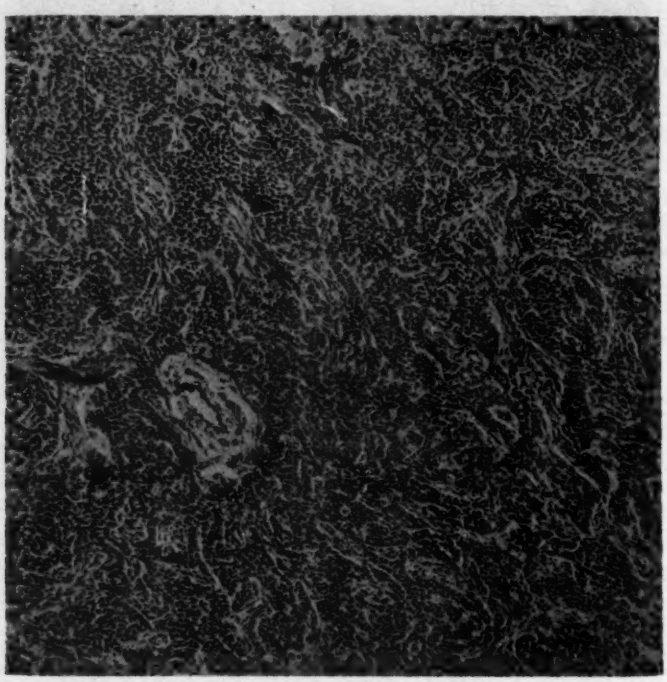

Fig. 2.—Photomicrograph of granulosa-cell tumor (ruptured) of Case 3. Finely trabecular and diffuse pattern, in some areas microfolliculoid, rare mitotic figure. (Hematoxylin and eosin. ×100.)

week baby. To date the patient's periods have been regular. Examinations of the breasts, abdomen, and pelvis have revealed no change. The uterus is slightly enlarged and thickened in its anterior-posterior diameter. This finding was noted at operation and remains unchanged. Recent premenstrual endometrial biopsy reveals secretory change and Papanicolaou smear shows premenstrual type cytology with a normal estrogenic activity as evidenced in the cornified cells.

Follow-up period of four years.

CASE 4 (March, 1948).—G. G., 35-year-old, white, gravida ii, para i, complained of a two-year history of pressure in the left lower abdominal quadrant. The menses had occurred every five to six weeks for the past three years, replacing the twenty-eight day cycle, and the amount of flow decreased from five to three days. There was a history of sterility for three years.

Operation consisted of curettage, total hysterectomy, salpingo-oophorectomy bilateral, and appendectomy. The left ovarian mass measured 6 by 4 by 3.5 cm. and revealed a rent in its capsule. The abdominal cavity contained an estimated 500 c.c. of fresh blood.

Pathologic Diagnosis.—Granulosa-cell tumor of left ovary with cystic degeneration, perforation of capsule, and intraperitoneal hemorrhage; granulosa-cell tumor in right

ovary probably metastatic, multiple follicle cysts of right ovary; total uterus (5 by 4 by 2.5 cm.) with endometrium in proliferative stage, chronic cervicitis with parakeratosis; Fallopian tubes.

Fig. 3.

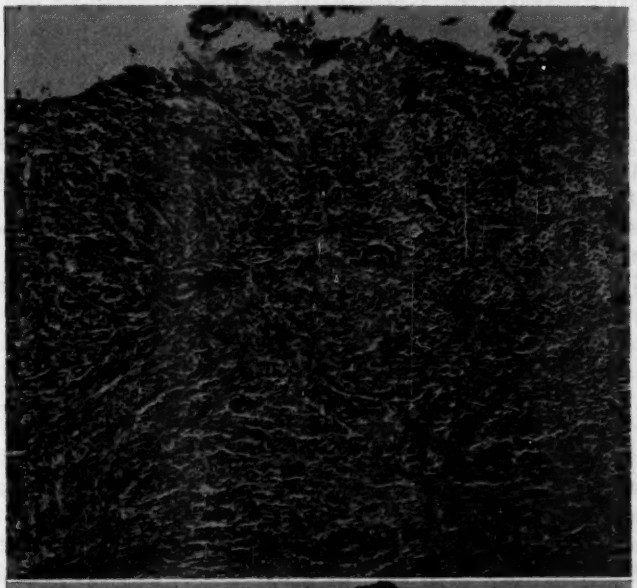

Fig. 4.

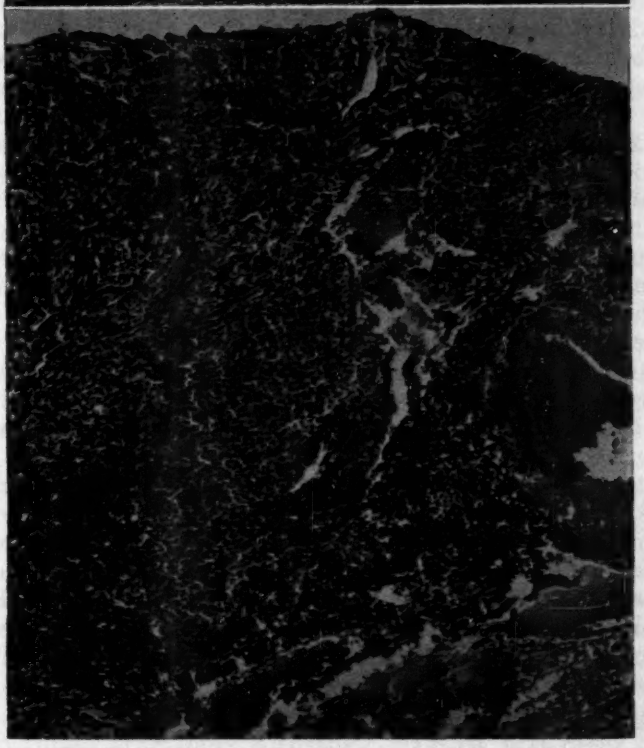

Fig. 3.—Photomicrograph of granulosa-cell tumor (ruptured) of Case 4. Diffuse and finely trabecular pattern. Occasional mitotic figures. (Hematoxylin and eosin. ×100.)

Fig. 4.—Photomicrograph of granulosa-cell tumor probably metastatic, Case 4. Diffuse pattern, occasional mitotic figures. Note ovarian tissue lower right. (Hematoxylin and eosin. ×100.)

The postoperative course was uneventful. Fractional x-ray therapy was given totaling 7,200 r surface dose, 3,456 r depth dose. Repeat follow-up examinations of breasts, abdomen, and pelvis have been negative. The patient is at present free of any menopausal symptoms despite the fact that no estrogenic therapy has been given. A recent Papanicolaou smear was postmenopausal in type with evidence of minimum estrogenic secretion. The general condition is excellent.

Follow-up period of two and three-fourths years.

Comment

In Case 1, it is regrettable that no photomicrographs are available. It was suggested by the operator that this small 1.5-cm. tumor was immature, microfolliculoid in type and doubtless had little estrogenic activity. There was no endometrial tissue for study or blood and urine determinations of estrogenic levels. The only suggestive evidence is the slight preoperative change in the menstrual cycle which readjusted following surgery. There was no immediate postoperative vaginal bleeding as one might anticipate with a mature active tumor. All the signs and symptoms might well be explained on the basis of her chronic pelvic inflammatory disease.

In Case 2, it does not seem indicated in this paper to discuss the vicissitudes of uterine perforation with a catheter. There are, in this case, again no data for judging estrogenic activity since the patient was 42 years old and her prior menses had always been infrequent and scanty. She admits having only one period four months following her operation. Again the tumor must be essentially immature in type and of probable limited estrogenic secretion.

Study of these cases and of the pertinent literature brings out certain facts of interest and of value. The tendency of granulosa-cell tumors to rupture with considerable hemorrhage is rarely mentioned in current studies of this neoplasm. A notable exception is found in the *Atlas of Ovarian Tumors* by Barzilai. She makes the following statement, "A severe intra-abdominal hemorrhage, due to rupture of the capsule of the tumor, is quite peculiar to granulosa cell tumors, and is not rare."[2] Bo von Friesen, in the Swedish literature, echoes the same feeling. He states that rupture is more common in granulosa-cell tumors than in any other type of ovarian neoplasm.[3] The architecture of these tumors is often characterized by a poor supporting framework for the granulosal elements.[4] They may tend to necrosis, marked cystic degeneration, and intracystic hemorrhage. Torsion and infarction have been reported.

In a review of the literature a total of twenty-five cases of rupture of the capsule of this neoplasm has been found with accompanying severe intra-abdominal bleeding.[3, 5-21] There are doubtless more cases and many as yet unreported. I know of three such cases, unreported, at the present time.[23, 24] The largest series noted was that of von Friesen[3] who reported seven cases of rupture in a total of fifty cases of granulosa-cell tumor found in Sweden. He also described ten cases gleaned from the literature.[14-22] Follow-up study of this type of neoplasm is difficult because of the well-known tendency of the growth to late recurrence. However, an attempt has been made to total all available reports of the entire twenty-five cases found of ruptured granulosa-cell tumor with bleeding. Information sought was that of follow-up record and tumor recurrence. There are pertinent data on fifteen cases of the twenty-five. They may be summarized as follows:

1. Ten patients living and well with no recurrences (two at two years, one at two and one-half years, one at two and three-fourths years, one at three years, one at four years, one at five years, one at seven years, two at ten years.)
2. One patient is living and well at seventeen years following two operations for recurrence at nine and eleven years, respectively.

3. Three patients died in four years or less (one of metastases to the brain and two of abdominal recurrence.)

4. One patient died in eight years of apparent pelvic recurrence.

The importance of late recurrence in cases with intact capsules has been stressed by Jones and Te Linde.[25] They report three Negro patients who died of recurrent granulosa-cell tumors eighteen, twenty, and twenty-one years following the primary operations. One case of this group is of particular clinical interest because of the tremendous quantity of fluid found in the abdominal and chest cavities prior to surgery. Four paracenteses yielded 19,500 c.c. from the abdomen and two thoracenteses yielded 2000 c.c. from the chest. At operation the tumor was only slightly adherent to the broad ligament and the capsule was intact. Aimes and his associates,[26] in the French literature, have recorded the excision of a retroperitoneal mass thirty-three years after primary removal of a granulosa-cell tumor from a girl 8 years of age. With such a long interval between the appearance of the two tumors one might ask if this retroperitoneal mass might not have been a primary granulosa-cell tumor of extraovarian origin. Five such tumors of extraovarian origin have been reported in the past thirteen years.[8, 27-30]

Case 3 of our present series is one of the few I could find recorded in which the patient delivered a living thirty-nine week baby following rupture of a granulosa-cell tumor with massive bleeding. Von Friesen reports a comparable case but the pregnancy terminated at seven months and the infant died.[3] Case 3 is clinically illustrative of a return of normal menses and fertility following removal of this type of neoplasm. Prior to operation the patient had been sterile for three and one-half years. Again this case presents at least one argument for conservative operation during the childbearing period. There are six fairly recent reports in the literature of granulosa-cell tumor coexisting with a pregnancy despite the usual findings of sterility in such cases.[31-36] It would appear that in these instances the tumor must have been primarily immature in type and a scant producer of estrogen.

Both Cases 3 and 4 in this series bring up the problem of the wisest surgical handling of granulosa-cell tumors, ruptured or unruptured, at the operating table. The gross appearance of this neoplasm is usually that of a round, lobulated, or kidney-shaped tumor varying greatly in size. The capsule is smooth and glistening and is bluish white, grey, or yellowish white. It may be solid, semisolid, or cystic. On cut section necrotic change and hemorrhage are frequent.[2] Cut surface may be yellow, gray pink, or may show an orange hue. Cystic degenerated zones are commonly encountered, chiefly in the large tumors.[37] Tumors that reveal penetration or perforation of the capsule, that tend to be adherent to adjacent structures, or that are found in association with other pelvic pathologic conditions, appear to carry a more grave prognosis. In those cases in which the tumor is found free with a smooth intact capsule, simple excision (salpingo-oophorectomy) is the procedure of choice especially in young women. It is usually conceded that total hysterectomy with removal of both adnexa is indicated in older women. However, von Friesen states that he found no recurrence in the pelvic organs per se.[3] It would seem, thus, that in older women who present a grave surgical risk conservative surgery may be employed. Follow-up records are not yet adequate to clarify this point entirely. In cases of ruptured granulosa-cell tumor the same rationale applies. If the retained tumor fragments keep their viability and recur there is still a chance for successful local excision due to the slow rate of growth and the usual relative benignity of this neoplasm. It cannot be stressed too strongly that operative handling of these tumors should be very gentle to avoid unnecessary rupture and hemorrhage in their removal.

Summary

1. A series of four granulosa-cell tumors occurring over a thirty-two-year period at the Methodist Hospital, Brooklyn, have been reported.

2. All four patients are living and well with no evidence of recurrence at twelve, eight, four, and two and three-fourths years.

3. Two cases (reported before) were reviewed of rupture of the capsule with marked intra-abdominal bleeding.

4. One case of granulosa-cell tumor was associated with a perforation of the uterus with a catheter.

5. Twenty-five cases of ruptured granulosa-cell tumors with intra-abdominal hemorrhage, twenty-three from the literature, were reviewed.

6. The salient clinical factors relative to the above are discussed.

I wish to express my appreciation to Drs. G. H. Davis, S. C. Hall, and P. A. Renaud for permitting use of their cases for this paper, and to Dr. B. Herr for his assistance in the interpretation of the micropathology.

References

1. French, W.: New York State J. Med. **49**: 2305, 1949.
2. Barzilai, G.: Atlas of Ovarian Tumors, New York, 1949, Grune & Stratton, p. 33.
3. von Friesen, B.: Acta obst. et gynec. Scandinav. **24**: 8, 1943.
4. Traut, H. F., and Marchetti, A. A.: Surg., Gynec. & Obst. **70**: 632, 1940.
5. von Friesen, B.: Acta obst. et gynec. Scandinav. **24**: 8, 1943.
6. Taussig, F. J.: Am. J. Cancer **15**: 1547, 1931.
7. Schultz, M.: Am. J. Obst. & Gynec. **26**: 627, 1933.
8. Compton, Beverly C.: Am. J. Obst. & Gynec. **34**: 85, 1937.
9. Vogt, C. J.: Am. J. Obst. & Gynec. **40**: 285, 1940.
10. Dockerty, M. B., and McCarty, W. C.: Am. J. Obst. & Gynec. **39**: 147, 1940.
11. Bach, A. C., and Montgomery, M. M.: J. Indiana M. A. **34**: 421, 1941.
12. Bianco, J. J., and Favorite, G. O.: Am. J. Obst. & Gynec. **52**: 677, 1946.
13. Brewer, A. C.: Brit. M. J. **1**: 49, 1948.
14. Klaften, E.: Arch. f. Gynäk. **150**: 643, 1932.
15. Deutsch, J.: Zentralbl. f. Gynäk. **57**: 651, 1933.
16. Lebowich, R. J.: Arch. Path. **15**: 747, 1933.
17. Schiller, Walter: Pathologie und Klinik der Granulosazell-tumoren, Wein, 1934, Wilhelm Mandrich, p. 197.
18. Habbe, K.: Zentralbl. f. Gynäk. **55**: 1088, 1931.
19. Klaften, E.: Zentralbl. f. Gynäk. **58**: 204, 1934.
20. Bagger, S. V.: Hospitalstid. **76**: 881, 1933.
21. Fauvet, E.: Zentralbl. f. Gynäk. **56**: 3088, 1932.
22. Sjövall, A.: Nord. med. tidskr. **11**: 759, 1936.
23. Howe, J.: Personal communication.
24. deVeer, A. J.: Personal communication.
25. Jones, G., and Te Linde, R.: Am. J. Obst. & Gynec. **50**: 691, 1945.
26. Aimes, A., Guibert, H., and Galvaing: Gynéc. et obst. **45**: 801, 1946.
27. Voight, W.: Am. J. Obst. & Gynec. **36**: 688, 1938.
28. Powell, Cuthbert, and Black, W.: Am. J. Obst. & Gynec. **40**: 318, 1940.
29. Ragins, A., and Frankel, L.: Am. J. Obst. & Gynec. **40**: 302, 1940.
30. Rottino, A., and Crown, C.: Am. J. Obst. & Gynec. **60**: 914, 1950.
31. Greenhill, J. T.: Year Book of Obstetrics and Gynecology, Chicago, 1947, The Year Book Publishers, Inc., p. 463.
32. Greene, G. G., Smith, A. E., and McClelland, T.: Am. J. Obst. & Gynec. **60**: 686, 1950.
33. Slamova, B.: Československ. gynaek. **16**: 358, 1937.
34. Henderson, D. N.: Am. J. Obst. & Gynec. **43**: 194, 1942.
35. Spencer, J. A., and Hollenbeck, Z.: Am. J. Obst. & Gynec. **54**: 281, 1947.
36. Falls, F., Ragins, A., and Goldenberg, M.: Am. J. Obst. & Gynec. **57**: 1107, 1949.
37. Dockerty, M. B.: S. Clin. North America **27**: 837, 1947.

502 Eighth Avenue

Discussion

DR. J. E. HALL.—It is of interest that in thirty-two years of a large hospital service, only four cases of granulosa-cell tumor were noted. It is rather difficult to understand why that should be. Recently, in reviewing the ovarian tumors at the Brooklyn Hospital in a five-year period, we came across three and I am sure if we went back further, we would run into more than four. It brings up the point of whether in the days before 1930 the pathologist correctly diagnosed these lesions. In a review of some of our work, going back into the early thirties and late twenties, many cases reported at that time as sarcoma of the ovary today would be reported as granulosa-cell tumor. I would like to call attention to the ages of the patients in this report. All four were under 42 years of age and yet, in most of the series reported, at least 65 per cent of all patients are past 50. I would like also to bring up the use of frozen section in ovarian tumors. We feel very inadequate at times in making a correct microscopic diagnosis of many of the ovarian neoplasms from frozen section. Often all we can say is, it is or it is not malignant.

The female hormones are steroids and as such are soluble in acetone. By the use of this fact, it has been demonstrated by histochemical procedures that the hormones of the granulosa-cell tumors are found in the luteinlike cells and not to any degree in the granulosa cells. Since many of these tumors contain few of these luteinlike cells, it is possible to have a granulosa-cell tumor producing very little estrogenic hormone and thus no hyperplasia of the endometrium and no abnormal uterine bleeding. Dr. French did not mention that symptom in any one of his four cases. I would like to emphasize another point: Luteinization and lipoid accumulation in the cells are not synonymous. Luteinization should produce a pregravid type of endometrium because of the progesterone. Most of these tumors do not produce progesterone, they produce estrogen, and it would be much better in discussing these tumors, certainly from the pathological viewpoint, to say we have pseudoluteinization rather than luteinization.

As Dr. French brought out, certainly not all these tumors are malignant and I think we should bear this in mind. Possibly no more than 25 per cent of these feminizing mesenchymomas are malignant but because recurrences may be found very late in life, all cases should be carefully followed for the duration of that individual's life. I believe we have fairly good evidence that both will run the same course and it is also very difficult to separate them histologically. In regard to therapy, I think conservative surgery in women under 40 can be safely used, whereas, in women over 40 radical surgery is the procedure of choice.

DR. EUGENE COLER.—I think that if sections are very carefully examined, more tumors of this kind will be discovered. I have seen several that were of minute size, only a few millimeters in diameter and occupying a tiny portion of an ovary. These can easily be missed if the ovaries are not completely examined and sectioned and this might be one reason why only 4 cases were found in thirty-two years. I feel that the incidence of granulosa-cell tumor is higher in the average hospital.

DR. FRENCH (Closing).—To answer Dr. Hall's comment concerning the investigative work of McKay, Robinson, and Hertig, it is interesting to note the fact that Traut and Marchetti found only one case that they considered to be a so-called "pure granulosa cell tumor" or in other words a tumor type in which the theca-cell component was present in a tremendously reduced ratio. Despite the reduced theca-cell content the tumor was rated as a marked producer of estrogenic substance.

I can offer no adequate explanation of the fact that only 4 cases of granulosa-cell tumor were found in our records. During the past few years our laboratory has been particularly attentive to the study of all ovarian neoplasms and multiple sections are cut of each tumor. It is an unfortunate but well-known fact that economic considerations and time factors preclude a truly exhaustive study of such neoplasms in the usual general hospital.

STUDIES ON THE URINARY EXCRETION OF "XANTHURENIC ACID" DURING NORMAL AND ABNORMAL PREGNANCY: A SURVEY OF THE EXCRETION OF "XANTHURENIC ACID" IN NORMAL NONPREGNANT, NORMAL PREGNANT, PRE-ECLAMPTIC, AND ECLAMPTIC WOMEN*

HERBERT SPRINCE, PH.D., RICHARD S. LOWY, B.S., CLAIR E. FOLSOME, M.D., AND JOHANNES S. BEHRMAN, M.B., CH.B.,** RARITAN, N. J.

(From the Division of Nutrition, Ortho Research Foundation)

THE importance of pyridoxine in preventing disturbances early in pregnancy has been pointed out by Willis and associates,[1] Weinstein and collaborators,[2, 3] and Silbernagel and Burt.[4] Recently Hobson[5] has presented evidence that a deficiency of intake or metabolic dysfunction of vitamin B_6 and nicotinic acid may be a predisposing factor in the genesis of toxemias in the later stages of pregnancy. Support for this idea is apparent in work on animals in which experimental pyridoxine deficiency has been found to produce conditions resembling those occurring in eclampsia.[6, 7, 8, 9]

Pyridoxine deficiency has been shown so to alter the course of tryptophane metabolism as to result in the urinary excretion of large amounts of an abnormal metabolite known as "xanthurenic acid (XA)."† This has been demonstrated to occur in the rat,[10, 11] mouse,[12] pig,[13] dog,[14] monkey,[15] and more recently in the human being after ingestion of a massive dose of tryptophane.[16]

In the light of the above observations we felt it would be of interest to determine whether "XA" could be detected in large amounts in the urine of pre-eclamptic and eclamptic women. In this connection, we undertook to survey five categories of female subjects, namely: (1) normal nonpregnant women, (2) normal pregnant women (early last trimester), (3) pre-eclamptic patients, (4) eclamptic patients, and (5) women in the last trimester of "normal" pregnancy with clinical complications due to concurrent disease.

It is the purpose of this paper, therefore, to present: (a) a method for the detection of the abnormal urinary excretion of "xanthurenic acid (XA)" in the human being and (b) data on the urinary excretion of "XA" of the five categories of female test subjects outlined above.

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*A preliminary announcement of this work appeared under the title of "Metabolic Patterns in Normal and Abnormal Pregnancy," in the scientific and educational exhibit of the International and Fourth American Congress on Obstetrics and Gynecology held in New York City, May 14-19, 1950, sponsored by the American Committee on Maternal Welfare, Inc.

**Present Address: Department of Obstetrics and Gynecology University of Michigan, Ann Arbor, Mich.

†"Xanthurenic acid (XA)" is defined in this paper as that material which produces a green color with the ferric ion in the method of assay described in the context. It should be noted that urine may contain other substances XA-like in character which might also possibly form a green color under the conditions of the test. To emphasize this point, we have enclosed xanthurenic acid in quotation marks.

Methods and Procedures

A. Principle of "XA" Excretion Test.—"XA" excretion arising from abnormal tryptophane metabolism can be detected in the urine of the human being only after the ingestion of a massive dose of dl-tryptophane.[16] This fact, coupled with the observation that fasting morning urine specimens may be of equal, if not greater, value than 24-hour urines in vitamin retention and excretion assays,[17, 18] led us to devise the following "XA" excretion test. Each test subject was followed for a period of seven consecutive days. For the first three days fasting morning urines (overnight fast) were obtained to establish the natural base line excretion of "XA." On the evening of the third day, a test dose of 10 Gm. of dl-tryptophane (mixed well into orange juice in the form of a cocktail) was ingested by the test subject just before retiring. Fasting morning urine specimens were then collected for four more successive days. The urines thus obtained were adjusted to slightly acid pH to prevent destruction of "XA," stored in bottles containing volatile disinfectant, and placed in the cold room. Assays for "XA" were carried out by a modification of the method of Rosen, Huff, and Perlzweig[19] discussed below.

B. Notes on the Collection and Storage of Fasting Morning Urines.—

a. Prior to commencing the test, test subjects were instructed to limit their last evening food intake for each day to the evening meal (6:00-7:00 P.M.) for the seven-day interim of the test. Before retiring the urine was voided as usual and discarded.

b. Each morning for the seven-day period, the fasting morning urines were collected in a nonmetal (preferably) or enameled container immediately after arising and before eating. (Exposure of the urine to metal containers may vitiate the test.)

c. Such urines freshly obtained were adjusted to pH 5.5-5.9 with either 5N HCl or 5N NaOH to insure stability of "XA."[10] Since relatively small quantities of urine were used in assay, 100-200 ml. specimens were stored in the cold in brown bottles containing a volatile preservative. Hutner's mixture[20] was found to be very effective for this purpose, although toluene or chloroform may be used equally as well.

d. To assay, 25-50 ml. of urine were adjusted to pH 7.8-8.1 with 5N NaOH and filtered; the volatile preservative was removed by an air jet. The filtered urine was then used for assay.

C. The Assay Procedure for "Xanthurenic Acid".—"Xanthurenic acid" was determined by the method of Rosen, Huff, and Perlzweig[19] adapted for use with an internal "XA" standard.[21] By such a procedure, corrections could be made for (a) the color of the reagents used and (b) the inherent color of the urine. It was found important to adjust all urine samples to pH 7.8-8.1 and to filter these before assay. Colorimetric measurements were made with the Evelyn photoelectric colorimeter with a 620 mμ filter which was found to fulfill the requirements of the Lambert-Beer law up to a concentration of 200 μg. of "XA" per 10 ml. assay tube.

In order to permit the rapid screening of urines in future surveys, a qualitative test paper was prepared (Ortho XA Test Paper), and a correlation was attempted between the test-paper method and the colorimetric test-tube procedure used routinely. The test paper consisted of a strip of absorbent acid-resistant filter paper impregnated with the necessary reagents. On immersion into urine, a green color was formed on the paper if the urine contained "xanthurenic acid."

D. Urine Specific Gravity.—Specific gravity tests were made on a number of these urines to determine the effect of dl-tryptophane intake.

Results and Comments

The results obtained for the five different categories of women examined are set forth below in a series of tables. It should be emphasized that two factors must be considered in evaluation of differences in "XA" excretion after tryptophane between normal test subjects and patients in various pathognomonic states:

1. The Q_{XA} value $=$ "XA" excretion on morning *after* feeding tryptophane (4th day) (μg./ml.) / "XA" excretion *before* tryptophane, 3-day average (μg./ml.)
2. The level of "XA" excretion (μg./ml.) for the entire seven-day period before and after dl-tryptophane.

The Q_{XA} value is generally the more reliable index of "XA" excretion since initial levels of "XA" excretion before tryptophane are likely to vary from day to day in a given test subject. In some instances, however, the initial "XA" excretion before tryptophane ingestion may be sufficiently high to result in a low Q_{XA}. When this is the case and inspection of the actual excretion values reveals a high "XA" excretion after tryptophane, it is reasonable to conclude that the test subject in question has demonstrated an abnormal "XA" excretion by virtue of her levels of "XA" excretion rather than by the Q_{XA} value.

Table I presents data for normal nonpregnant test subjects.

TABLE I. URINARY "XANTHURENIC ACID" EXCRETION TEST VALUES OF NORMAL NONPREGNANT TEST SUBJECTS

	μG. "XA"/ML. FASTING MORNING URINE								Q_{XA}	RESPONSE TO XA TEST PAPER	
	BEFORE TRYPTOPHANE				AFTER TRYPTOPHANE						
TEST SUBJECT	1ST DAY	2ND DAY	3RD DAY	AVERAGE FOR 3 DAYS (BT)	4TH DAY (AT)	5TH DAY	6TH DAY	7TH DAY	$\left(=\frac{AT}{BT}\right)$	3RD DAY (BT)	4TH DAY (AT)
M. T.	50.6	39.7	41.4	43.9	27.3	11.5	32.6	23.6	0.6	(-)	(-)
L. F.	16.5	1.8	6.7	8.3	7.8	19.3	5.0	3.2	0.9	(-)	(-)
F. R.	31.5	17.0	15.4	21.3	20.2	19.8	17.7	25.6	1.0	(-)	(-)
R. R.	20.9	10.3	9.5	13.6	24.6	5.1	10.4	7.4	1.8	(-)	(-)
D. Z.	14.4	6.5	7.6	9.5	8.6	12.6	13.7	4.6	0.9	(-)	(-)
M. R.	15.6	2.3	4.6	7.5	32.6	5.0	12.4	18.0	4.4	(-)	(-)
Average	24.9	12.9	14.2	17.4	20.2	12.2	15.3	13.7			

Average $Q_{XA} = \frac{20.2}{17.4} = 1.2$

From the table, it is obvious that the *average* base line excretion of "XA" for the first three days prior to tryptophane ingestion was 17.4 μg./ml. of urine. No appreciable rise in excretion occurred after feeding tryptophane as is apparent from the *average* value of 20.2 μg./ml. of urine. The *average* Q_{XA} value was 1.2. The "XA" test paper gave negative results. The range of "xanthurenic acid" excretion before tryptophane in a series of six normal nonpregnant women varied between 1.8 and 50.6 μg./ml. of urine. This was taken to be the normal range in the evaluation of the other test subjects.

Data obtained for normal pregnant women in the last trimester of pregnancy are presented in Table II.

The *average* base line "XA" excretion of the test subjects in Table II for the first three days before tryptophane was 22.9 μg./ml. of urine. On the morning after tryptophane ingestion, an appreciable rise in "XA" excretion was noted, the *average* value being 41.0 μg./ml. The *average* Q_{XA} value was 1.8.

Determinations with XA test paper were all negative. It is interesting to note that one test subject, M. H., exhibited an abnormally high base line excretion before tryptophane (average for 3-day period, 61.9 μg./ml.). Her Q_{XA} value, however, was within normal limits and the course of her pregnancy was uneventful. It is possible, therefore, that the diet of this individual may have been low in vitamin "B" complex. Excluding test subject M. H., the range of "XA" excretion *before tryptophane* for seven normal pregnant women varied from 4.6 to 28.9 μg./ml.

TABLE II. URINARY "XANTHURENIC ACID" EXCRETION TEST VALUES OF NORMAL PREGNANT WOMEN

	μG. "XA"/ML. FASTING MORNING URINE								Q_{XA}	RESPONSE TO XA TEST PAPER	
	BEFORE TRYPTOPHANE				AFTER TRYPTOPHANE						
TEST SUBJECT	1ST DAY	2ND DAY	3RD DAY	AVERAGE FOR 3 DAYS (BT)	4TH DAY (AT)	5TH DAY	6TH DAY	7TH DAY	$\left(=\frac{AT}{BT}\right)$	3RD DAY (BT)	4TH DAY (AT)
M. S.	14.9	5.7	13.7	11.4	15.1	14.5	12.4	8.5	1.3	(-)	(-)
G. G.	15.3	13.2	9.9	12.8	32.6	7.1	31.0	12.2	2.6	(-)	(-)
M. W.	16.8	28.9	27.2	24.3	41.8	9.2	16.3	14.1	1.7	(-)	(-)
I. K.	27.0	27.4	20.4	24.9	39.3	43.0	19.5	24.4	1.6	(-)	(-)
V. M.	8.4	22.3	5.0	11.9	34.4	8.8	10.8	1.9	2.9	(-)	(-)
R. W.	13.5	20.2	4.6	12.8	15.7	6.7	20.8	5.0	1.2	(-)	(-)
M. H.*	58.9	37.4	89.5	61.9	108.0	38.6	7.6	19.8	1.7	(-)	(-)
Average	22.1	22.2	24.3	22.9	41.0	18.3	16.9	12.3			

$$\text{Average } Q_{XA} = \frac{41.0}{22.9} = 1.8$$

*Note abnormally high "XA" excretion prior to tryptophane intake.

The values obtained for a series of pre-eclamptic patients are set forth in Table III.

TABLE III. URINARY "XANTHURENIC ACID" EXCRETION TEST VALUES OF PRE-ECLAMPTIC PATIENTS

	μG. "XA"/ML. FASTING MORNING URINE								Q_{XA}	RESPONSE TO XA TEST PAPER	
	BEFORE TRYPTOPHANE				AFTER TRYPTOPHANE						
TEST SUBJECT	1ST DAY	2ND DAY	3RD DAY	AVERAGE FOR 3 DAYS (BT)	4TH DAY (AT)	5TH DAY	6TH DAY	7TH DAY	$\left(=\frac{AT}{BT}\right)$	3RD DAY (BT)	4TH DAY (AT)
H. M.	33.7	18.1	18.4	23.4	268.6	272.2	238.2	16.0	11.5	(-)	(+++)
H. C.	21.1	22.5	20.3	21.3	116.4	166.9	—	8.6	5.5	(-)	(++)
M. L.	8.6	9.2	5.5	7.8	210.6	78.0	112.0	142.0	27.0	(-)	(++)
J. L.	18.6	3.0	8.3	10.0	81.0	—	24.3	20.9	8.1	(-)	(+)
J. H.	—	8.2	2.1	5.2	261.5	8.1	4.7	8.9	50.3	(-)	(++++)
O. M.	17.8	6.2	1.6	8.5	234.2	9.2	4.5	11.8	27.6	(-)	(+++)
G. C.	8.9	7.7	17.3	11.3	225.0	13.7	10.9	7.1	19.9	(-)	(++)
Average	18.1	10.7	10.5	12.5	199.6	91.4	65.8	30.8			

$$\text{Average } Q_{XA} = \frac{199.6}{12.5} = 16.0$$

Here, again it is evident that prior to tryptophane intake the *average* base line "XA" excretion (12.5 μg./ml.) was apparently well within the normal range. "XA" excretion on the morning after tryptophane ingestion was, however, *markedly increased* (*average value*, 199.6 μg./ml.). Calculation of the

average Q_{XA} gave a value of 16.0. The XA paper test was consistently positive; varying degrees of color intensity were obtained corresponding to the quantitative variation in "XA" excretion.

The results found with eclamptic patients are shown in Table IV.

TABLE IV. URINARY "XANTHURENIC ACID" EXCRETION TEST VALUES OF ECLAMPTIC PATIENTS

	μG. "XA"/ML. FASTING MORNING URINE								Q_{XA}	RESPONSE TO XA TEST PAPER	
	BEFORE TRYPTOPHANE				AFTER TRYPTOPHANE						
TEST SUBJECT	1ST DAY	2ND DAY	3RD DAY	AVERAGE FOR 3 DAYS (BT)	4TH DAY (AT)	5TH DAY	6TH DAY	7TH DAY	$\left(=\frac{AT}{BT}\right)$	3RD DAY (BT)	4TH DAY (AT)
D. G.	27.5	8.5	9.4	15.1	134.6	8.9	11.5	6.8	8.9	(-)	(+)
J. G.	6.8	7.3	3.0	5.7	116.0	32.1	10.2	—	20.4	(-)	(++)
E. H.	14.7	11.4	10.3	12.1	221.0	9.8	6.3	12.8	18.3	(-)	(++)
Y. G.	40.3	40.1	21.3	33.9	145.4	6.0	15.8	8.8	4.3	(-)	(+)
B. S.	11.0	11.0	10.2	10.7	290.0	6.2	2.4	—	27.1	(-)	(+++)
Average	20.1	15.7	10.8	15.5	181.4	12.6	9.2	9.5			

$$\text{Average } Q_{XA} = \frac{181.4}{15.5} = 11.7$$

The values obtained with eclamptic patients are similar to those observed with the pre-eclamptic group. The *average* base line "XA" excretion before tryptophane was normal (15.5 μg./ml.); "XA" excretion rose greatly after tryptophane feeding (*average value*, 181.4 μg./ml.). The *average* Q_{XA} was 11.7. Consistently positive results were obtained with the XA test paper. These data correlated well with the quantitative colorimetric test-tube determinations.

Table V presents data of women in the last trimester of normal pregnancy with histories of concurrent pathognomonic disturbances.

In this series, it will be noted that normal base-line values were obtained *before* tryptophane intake as in previous instances. After tryptophane intake, large amounts of "XA" were excreted, but considerable variation of the increased levels was observed depending on the clinical condition of a given patient. Several of these patients presented one or more signs characteristic of pre-eclampsia although the classical symptoms did not develop at any time.

Two patients, M.O. and D. F., are worthy of detailed comment. Urines from both of these patients were sent to us as normal pregnant test subjects. Both gave a positive test for "XA." Eventually, it was found that M. O. had showed signs of excessive weight gain at the time the urine test was carried out. She was placed on a low salt diet and given ammonium chloride. The course of her pregnancy was uneventful thereafter, and a normal delivery resulted. The urine from patient D. F. gave an exceedingly high "XA" value after tryptophane. Not long after this test and just before delivery, D. F. developed signs of pre-eclampsia which continued for some time in the postpartum period. On the reconsideration of case histories, M. O. was reclassified as a possible pre-eclamptic, and D. F. as a definite pre-eclamptic. It would appear, then, that the increased "XA" excretion coincided with or predated the development of signs in these two cases.

Discussion

From the foregoing it is evident that *marked* increases in "xanthurenic acid (XA)" could be detected after tryptophane intake in the fasting morning urine of pre-eclamptic and eclamptic patients. In normal pregnant women, only

TABLE V. URINARY "XANTHURENIC ACID" EXCRETION TEST VALUES OF WOMEN IN LAST TRIMESTER OF NORMAL PREGNANCY WITH CLINICAL HISTORIES OF CONCURRENT DISEASE

TEST SUBJECT	CLINICAL DIAGNOSIS	μG. "XA"/ML. FASTING MORNING URINE								Q_{XA} $\left(=\frac{\text{AT}}{\text{BT}}\right)$	RESPONSE TO XA TEST PAPER	
		BEFORE TRYPTOPHANE				AFTER TRYPTOPHANE						
		1ST DAY	2ND DAY	3RD DAY	AVERAGE FOR 3 DAYS (BT)	4TH DAY (AT)	5TH DAY	6TH DAY	7TH DAY		3RD DAY (BT)	4TH DAY (AT)
J. S.	Rheumatic heart disease	6.2	8.6	6.7	7.2	597.3	9.6	11.7	3.5	83.0	(-)	(++++)
R. O.	Rheumatic heart disease	7.4	3.7	3.4	4.8	388.3	11.3	8.2	7.7	80.9	(-)	(++++)
M. O.	Possible pre-eclampsia	21.0	19.4	23.4	21.3	169.0	17.1	24.5	30.0	7.9	(-)	(+)
D. F.	Pre-eclampsia	4.7	1.6	10.4	5.6	1823.0	7.1	11.3	10.8	325.5	(-)	(++++)
L. B.	Thrombocytopenic purpura	17.1	29.9	2.9	16.6	1875.5	4.7	9.5	7.1	113.0	(-)	(++++)
W. S.	Pulmonary tuberculosis	17.5	22.8	12.8	17.7	1300.0	20.7	9.9	14.1	73.5	(-)	(++++)
L. W.	Moderate hypertension, with cardiac decompensation	2.3	—	7.6	5.0	44.7	2.0	4.7	6.6	8.9	(-)	(+)

a slight rise was noted, whereas normal nonpregnant women exhibited no change at all. That this effect was not specific for toxemias of pregnancy is apparent from Table V. The possibility exists, however, that the "XA" excretion test may be of value in the early detection of pre-eclampsia and eclampsia. This would appear to be so from the observation that two apparently normal pregnant women who gave high "XA" values, coincidently or eventually developed signs of eclamptogenic toxemias.*

The question may be raised as to the advisability of using 24-hour urine specimens in preference to the overnight-fasting morning urine specimens used in this investigation. In the foregoing study, it was felt that fasting morning urines presented two advantages: (1) elimination of the problem of urine collection in ambulatory test subjects, and (2) the first approximation of such specimens to the resting endogenous metabolism of a given individual. Obviously, however, 24-hour urine specimens possess distinct sampling advantages and should be made when conveniently possible.

The reliability of the test procedure described above rests on two factors, namely, (1) care in obtainment of the fasting morning urines and (2) the validity of the "XA" assay. The first point presents no problem if a reasonable degree of precaution is taken to follow directions; the second point, however, is worthy of a few further comments. The presence of blood in the urine may invalidate the assay. Care must be taken, therefore, to obtain urine samples free from blood. The deep brown color which often occurs in the urine after tryptophane ingestion does not generally interfere with the test. The maintenance of rigid pH control between 7.8 and 8.1 during assay, and the precise timing of the galvanometer readings (about 45 seconds after adding ferric ion) are factors which make for a more accurate assay. It is important to remember, also, that "xanthurenic acid" in this paper has been defined as that material which produces a green color with the ferric ion under the test conditions set forth. That this green color may be due not only to pure "XA" but also to other "XA"-like substances which may occur in urine should not be overlooked. It is important to emphasize, however, that by the procedure described in the foregoing, we have been able to detect *differences* in excretion values of "XA" or "XA"-like substances in the urines of patients with pre-eclampsia, eclampsia, and other clinical disturbances concurrent with "normal" pregnancy, from those of normal test subjects in the pregnant or nonpregnant state.

It is probable that the time required for the "XA" excretion test might be reduced to two days by obtaining, for example, one fasting morning urine *before* tryptophane ingestion and a second fasting morning urine *after* tryptophane ingestion. However, for the purpose of establishing the validity of this test, it was felt advisable to follow a given test subject for a period of seven days.

Specific gravity determinations of urines before and after tryptophane of a number of test subjects in the categories listed above ruled out the possibility that the high "XA" values in toxemias were the result of a concentration effect due to antidiuresis. Although, as would be expected,[22] the specific gravities of the urines of the pre-eclamptic and eclamptic patients *under treatment* were definitely less than those of the normal test groups, no appreciable change in the specific gravity of urine of any patient or test subject (toxemic or normal) occurred as a result of tryptophane ingestion. Such findings serve to corroborate further the evidence obtained from the three-day base-line "XA" excretion

*It is important to note that no attempt has been made in this study to determine the exact time of onset of increased "XA" excretion within the pregnancy period of those women exhibiting high values after tryptophane ingestion. It is possible that increased "XA" excretion may be a function of time within the pregnancy period serving as an indication of proximity to term even in normal pregnant women. This point must yet be fully investigated before categorical significance can be attached to increased "XA" excretion in eclamptogenic toxemias.

values *before tryptophane*. Thus, if a concentration effect were operating during "XA" excretion in the toxemias, we should expect higher base-line values *before tryptophane* for the pre-eclamptic and eclamptic patients than for the women in the normal nonpregnant and normal pregnant group. This, however, was not the case, as can be seen from the preceding tables. It is reasonable, therefore, to suppose that the high "XA" excretion *after* tryptophane ingestion is a true metabolic effect rather than an epiphenomenon of an abnormal urine concentration effect.

The significance of increased "xanthurenic acid" excretion in eclamptogenic toxemias is a matter for speculation. It is possible that a deranged protein metabolism known to occur in such conditions[23] may increase the metabolic demand for vitamin B_6 far beyond the normal optimal level of intake. The slow lysis of fibrin clots which may be constantly occurring may further increase the demand for pyridoxine, thereby predisposing toxemic patients towards a positive test for "XA." In this connection, it is interesting to note that fibrin is a protein known to be high in tryptophane content. It is possible, then, that high "XA" values reflect a double derangement of metabolic function: (1) abnormal vitamin B_6-niacin-protein metabolism and (2) excessive fibrinolytic activity in the maternal system. Finally, it may be worthy of note that, chemically speaking, XA bears a structural resemblance to cinchoninic acid and its derivatives, compounds which have been demonstrated recently to possess antidiuretic activity.[24, 25, 26, 27] and to cause an increased excretion of uric acid in man.[28, 29]

Summary

1. A "xanthurenic acid (XA)" excretion test has been described, based on the observation that urinary "xanthurenic acid" levels are best determined in the human being after ingestion of a massive dose of dl-tryptophane, according to the method of Greenberg and co-workers.[16] Each test subject was followed for a period of seven consecutive days. Fasting morning urines were obtained for three days before tryptophane ingestion and four days after tryptophane ingestion.

2. The "XA" assay employed was the method of Rosen, Huff, and Perlzweig adapted for use with an internal "XA" standard.

3. Data are presented to show that pre-eclamptic and eclamptic patients after ingestion of a 10-Gm. test dose of dl-tryptophane excreted much larger amounts of "XA" in the urine than did normal nonpregnant and normal pregnant women under the same conditions. A test paper has been devised which permits qualitatively the rapid detection of increased "XA" excretion.

4. The marked increase in "XA" excretion after feeding dl-tryptophane was shown not to be due to a specific disease entity since women with certain clinical disturbances in "normal" pregnancy also gave high "XA" values under the same test conditions. The possibility does exist, however, that the "XA" excretion test may be of value in the early detection of pre-eclampsia and eclampsia.

5. From a theoretical standpoint, it is possible that high "XA" values after tryptophane reflect a double derangement of metabolic function: (a) abnormal vitamin B_6-niacin-protein metabolism, and (b) excessive fibrinolytic activity in the maternal system. Moreover, chemically, "XA" bears a structural resemblance to cinchoninic acid and its derivatives, compounds which have been demonstrated recently to possess antidiuretic activity.

Addendum

After this work had been completed we were able to demonstrate by spectrophotometric means that the green color measured was due to xanthurenic acid. A rigorously quantitative assay for "XA" in urine based on "XA" recovery values varying within 100 per cent ± 15 has since been developed. Preliminary tests by this new method have further established the validity of the high Q_{XA} values obtained by the present method for preeclamptic and eclamptic patients. Details of this new procedure will appear in print elsewhere.

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References

1. Willis, R. S., Winn, W. W., Morris, A. T., Newson, A. A., and Massey, W. E.: Am. J. Obst. & Gynec. **44**: 265, 1942.
2. Weinstein, B. B., Mitchell, G. J., and Sustendal, G. F.: Am. J. Obst. & Gynec. **46**: 283, 1943.
3. Weinstein, B. B., Wohl, Z., Mitchell, G. J., and Sustendal, G. F.: Am. J. Obst. & Gynec. **47**: 389, 1944.
4. Silbernagel, W. M., and Burt, O. P.: Ohio State M. J. **39**: 1113, 1943.
5. Hobson, W.: J. Hyg. **46**: 198, 1948.
6. Chick, H., Macrae, T. F., and Worden, A. N.: Biochem. J. **34**: 595, 1940.
7. Calder, R. M.: J. Exper. Med. **79**: 215, 1944.
8. Patton, R. A., Korn, H. W., and Longenecker, H. E.: J. Biol. Chem. **152**: 181, 1944.
9. Richards, M. B.: Brit. M. J. **1**: 433, 1945.
10. Lepkovsky, S., and Nielsen, E.: J. Biol. Chem. **144**: 135, 1942.
11. Lepkovsky, S., Roboz, E., and Haagen-Smit, A. J.: J. Biol. Chem. **149**: 195, 1943.
12. Miller, E. C., and Bauman, C. A.: J. Biol. Chem. **157**: 55, 1945.
13. Cartwright, G. E., Wintrobe, M. M., Jones, P., Lauritsen, M., and Humphreys, S.: Bull. Johns Hopkins Hosp. **65**: 35, 1944.
14. Axelrod, H. E., Morgan, A. F., and Lepkovsky, S.: J. Biol. Chem. **160**: 155, 1945.
15. Greenberg, L. D., and Rinehart, J. F.: Federation Proc. **7**: 157, 1948.
16. Greenberg, L. D., Bohr, D. F., McGrath, H., and Rinehart, J. F.: Arch. Biochem. **21**: 237, 1949.
17. Najjar, V. A., and Holt, L. E., Jr.: Bull. Johns Hopkins Hosp. **69**: 476, 1941.
18. Holt, L. E., Jr., and Najjar, V. A.: Fed. Proc. Am. Soc. Exper. Biol. Part 2 **1**: 117, 1942.
19. Rosen, F., Huff, J. W., and Perlzweig, W. A.: J. Nutrition **33**: 561, 1947.
20. Hutner, S. H., and Bjerknes, C. A.: Proc. Soc. Exper. Biol. & Med. **67**: 393, 1948.
21. Johnson, B. C.: Methods of Vitamin Determinations, Minneapolis, 1948, Burgess Publishing Co., pp. 60-62.
22. Dieckmann, W. J.: The Toxemias of Pregnancy, St. Louis, 1941, The C. V. Mosby Company, p. 157.
23. Arnell, R. E., Goldman, D. W., and Bertucci, F. J.: J. A. M. A. **127**: 1101, 1945.
24. Marshall, E. K., Jr., and Blanchard, K. C.: J. Pharmacol. & Exper. Therap. **95**: 185, 1949.
25. Marshall, E. K., Jr., Blanchard, K. C., and Dearborn, E. H.: Bull. Johns Hopkins Hosp. **86**: 89, 1950.
26. Dearborn, E. H.: Bull. John Hopkins Hosp. **87**: 328, 1950.
27. Blanchard, K. C., Dearborn, E. H., Maren, T. H., and Marshall, E. K., Jr.: Bull. Johns Hopkins Hosp. **86**: 83, 1950.
28. Nicolaier, A., and Dohrn, M.: Deutsches Arch. f. klin. Med. **93**: 331, 1908.
29. Berlingozzi, S., and Donatelli, G.: Boll. Chim. Farm. **75**: 387, 1936.

ENDOCRINE FACTORS IN CANCER OF THE CERVIX UTERI

H. E. Nieburgs, M.D., Augusta, Ga.

(From the Department of Clinical Cytology, Medical College of Georgia)

THE junction of the squamous and columnar epithelium of the cervix is the site of continuous regenerative processes. Destruction of the junctional squamous epithelium leads to replacement by the columnar cells from the endocervix. This is clinically evident by "erosion." According to Meyer,[1] squamous epithelium may grow above or under the columnar cells, in which case healing of the erosion occurs. The newly formed epithelium consists first solely of basal and parabasal cells. Further growth of additional cellular strata establishes normal squamous epithelium. On the other hand, proliferation of the reserve cells may occur with loss of secretory activity that may develop into an undifferentiated regenerative epithelium. This, in turn, may undergo squamous metaplasia and thus change into normal epithelium.

Not infrequently, however, squamous metaplasia changes into neoplasia and constitutes at first a carcinoma in situ. A carcinoma may also develop from the squamous epithelium by the way of basal-cell proliferation or through intraepithelial anaplasia.[2] It is postulated that carcinoma in situ, if untreated or inadequately treated, changes to an invasive carcinoma. On the basis of this, the term "preinvasive carcinoma" has recently been increasingly used in place of carcinoma in situ. Whether the noninvasive cancer always changes into an invasive cancer is as yet uncertain. Similarly unknown is the period of latency, i.e., the length of time for invasion to occur.

Pathogenesis of Cervical Cancer

It was frequently suggested that cancer of the cervix was due to chronic cervicitis or to chronic irritation subsequent to injuries of parturition. Later it appeared reasonable to assume that the suggested predilection of cervical cancer for multiparas was not due to the traumatizing effects of delivery, but to excessive hormone stimulation to which the cervix is exposed in each pregnancy. The hyperplastic changes in the histological sections of cervices from pregnant women appeared to corroborate this hypothesis.[3] Histological and cytological studies of cervical epithelium under conditions of varied endocrine changes in the human being and animal suggest that growth of the cervical epithelium is under direct control of the hormones.[4-9] The morphogenetic changes which may lead to cancer are apparently caused by abnormal conditions of glandular function or hormone metabolism.

Proliferation of the squamous epithelium of the cervix is caused by estrogen and a pituitary factor[10] derived apparently from the acidophile cells of the anterior lobe.[11] With a change in pituitary function, growth of the squamous epithelium of the cervix appears to be decreased in spite of unchanged estrogen activity.[10] Progestogen has the effect of removing the upper layer of the cells from the cervical epithelium,[12] while testosterone derived from the adrenal

cortex produces mucification if moderately increased,[13] and a marked increase in the level of testosterone causes inhibition to the proliferative effect of estrogen.[14] Thus normal growth of the cervical epithelium depends at least on a normal pituitary-ovarian-adrenal-cortical interrelationship. (Figs. 1-4.)

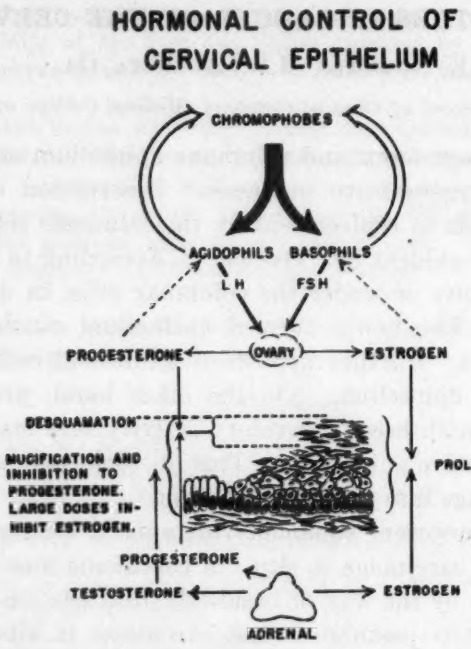

Fig. 1.—The effect of estrogen, progestogen, and testosterone on the cervical epithelium.
——→ Stimulation.
- - - - - - - → Inhibition.

There is increased growth during the follicular phase under the effect of estrogen and a further growth increase with marked desquamation during the luteal phase due to the combined action of estrogen and progestogen. A slight decrease in estrogen activity presents a continuous growth stimulus to the cervical epithelium. A marked decrease in the estrogenic level is, on the other hand, followed by reduced epithelial growth. During menopause, ovarian deficiency produces changes in the endocrine system which, in turn, influence the growth of the cervical epithelium. Atrophy occurs in such conditions in which a persistent decrease in the estrogenic level occurs. If, after cessation of ovarian function, estrogen production is taken over by the adrenal cortex, a continuous growth stimulus is being exerted on the cervical epithelium. It thus appears that normal cellular growth of the cervical epithelium is only maintained as long as normal physiological conditions prevail, such as cyclic fluctuation in the estrogen-progestogen levels during childbearing age and a decrease in the estrogenic level after menopause. It is therefore postulated that the continuous stimulating effect of estrogen uninterrupted by progestogen may be inimical to the cervical epithelium.

Procedure of Investigation

The routine examination of about 30,000 women by endocervical smears for the detection of cervical cancer carried out by this department through physicians' offices and University Hospital clinics made the diagnosis of a large number of cases possible. The first 100 cases of preinvasive cervical cancer and

100 cases of invasive cervical cancer were tabulated according to various criteria and the data of both groups were compared.

Period of Latency.—The average age of patients with preinvasive cancer was compared with the average of the group with invasive cancer as reported in previous publications. It appeared that the average age for preinvasive cancer

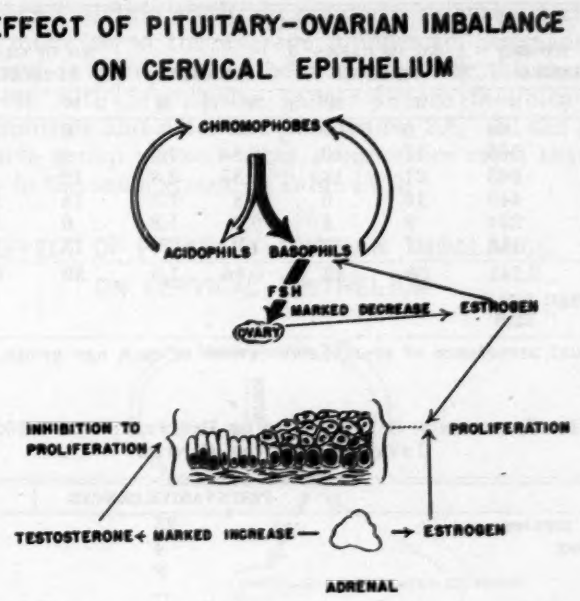

Fig. 2.—The effect of marked estrogen deficiency on the cervical epithelium.

is 39.2, while that for invasive cancer is 50.3, resulting in a difference of 11.1 years. It was therefore concluded that this was the approximate average time required for a preinvasive cancer to become invasive.[15, 16] A more detailed breakdown into age groups revealed that the greater incidence of preinvasive cancer was present in the younger women between 30 and 39 years of age, while invasive cancer occurred mainly in the age group of 40 to 49 years, and past the age of 60 years. This, however, presented an erroneous conclusion since a breakdown into age groups of the total number of women screened revealed that preinvasive cancer during the ages of 30 to 39 years appeared prevalent due to the fact that a larger number of women was screened in this age group. (Table I.)

The number of preinvasive cancer cases, if considered in relation to the number of women screened, therefore, shows an almost equal incidence in all decades of life, while cases of invasive cancer appear to increase in number with each decade.[17] Hence it is suggested that the average age of patients with preinvasive cancer is probably higher if derived from screening of equal numbers of women in each age group. As a result of this, the average age difference between preinvasive and invasive cancer is apparently less than previously reported. This is more in keeping with the clinical results of Glatthaar,[18] Wespi,[19] and our own experience.[20] Furthermore, the constant prevalence of preinvasive cancer in all age groups and increase of invasive cancer with each decade indicates a decrease in the average age difference with increasing age.

Complaints.—In the preinvasive group only nine patients had complaints directly related to cervical pathology, while most complaints are apparently due to decreased estrogen activity. In the invasive group, 54 patients had

complaints related to the cervix. Groups composed entirely of white patients would have probably produced a higher rate of complaints directly related to the cervix in cases of invasive cancer. (Table II.)

TABLE I. THE INCIDENCE OF CARCINOMA OF THE CERVIX UTERI* (10,000 CASES)

AGE GROUPS	NO. OF WOMEN SCREENED		PREINVASIVE NO. OF CASES DETECTED		PREINVASIVE PER CENT		INVASIVE NO. OF CASES DETECTED		INVASIVE PER CENT	
	W	N	W	N	W	N	W	N	W	N
-18	110	64	0	0	—	—	0	—	—	—
19-29	2,008	585	17	10	0.84	1.7	4	3	0.2	0.5
30-39	2,462	663	21	19	0.85	2.8	12	7	0.48	1.0
40-49	1,991	449	16	6	0.8	1.3	15	19	0.75	4.2
50-59	993	234	9	4	0.9	1.8	6	15	0.6	6.0
60-	548	146	7	3	1.2	2.0	13	16	2.3	10.9
	8,112	2,141	70	42	0.86	1.9	50	60	0.6	2.8
	Average age									
	39	32.6								

*Note the equal prevalence of preinvasive cancer in each age group. W = White. N = Negro.

TABLE II. COMPLAINTS IN 100 CASES OF PREINVASIVE AND 100 CASES OF INVASIVE CERVICAL CANCER*

	PREINVASIVE CANCER	INVASIVE CANCER
Irregular menses	25	26
Amenorrhea	4	2
Spotting	9	–
Bleeding	–	54
Discharge	13	3
Nonovulatory cycle	15	–
Protracted low estrogen activity	9	2
Sterility	16	8
Lower abdominal pain	17	–
Ovarian cyst	2	1
One ovary previously removed	5	5
Early menopause	10	21
No complaints	34	–

*These are the principal complaints and symptoms. Protracted low estrogen activity is reported as that in nine cases only, but was usually associated with all functional disorders listed.

Estrogen Activity.—More light was shed on the nature of complaints apparently due to estrogen deficiency through studies on estrogen activity as determined by cytological examination. In the premenopausal group of both preinvasive and invasive cancer, 71 per cent showed estrogen deficiency, while of the postmenopausal cases the majority showed increased estrogen activity. (Table III.) This increase in the estrogenic level, however, is only relative and corresponds to the decreased level of the premenopausal group. Essentially, both the premenopausal and postmenopausal patients showed a high incidence of protracted low estrogen activity.

TABLE III. ESTROGEN ACTIVITY IN PATIENTS WITH CERVICAL CANCER* (PER CENT)

	PREMENOPAUSAL		POSTMENOPAUSAL	
	DECREASED	INCREASED	DECREASED	INCREASED (RELATIVE)
Preinvasive cancer	71	3.2	30	70
Invasive cancer	71	6.2	26.4	63.6

*Increased estrogen activity past the menopause is relative and corresponds to moderately decreased estrogen activity during the childbearing age.

The Role of Pregnancies in the Genesis of Cervical Cancer

It has frequently been suggested that multiple pregnancies enhance the development of cervical cancer.[21] This effect of pregnancies was explained by the excessive stimulating action of hormones on the cervix for a continuous period of nine months.

The data on hand of this study do not seem to support this theory. An investigation was made as to the average number of pregnancies in patients with preinvasive and invasive cancer before and after the menopause, and it appeared that those with preinvasive cancer before the menopause, had an average of 2 pregnancies and after the menopause 2.8. In the postmenopausal patients the invasive group showed three pregnancies more than patients with preinvasive cancer in the same group. (Table IV.)

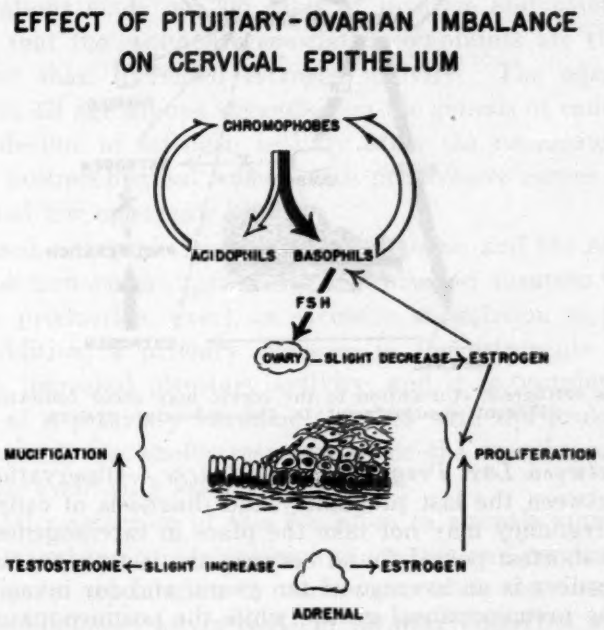

Fig. 3.—During childbearing age, a slight decrease in estrogen activity produces a continuous growth stimulus to the cervical epithelium.

In order to evaluate the significance of the number of pregnancies in cancer patients, these would have to be compared with a similar number and type of women apparently free of cancer. Certain observations, however, cast some doubt on the contributing factor of pregnancies in the genesis of cervical cancer. The large percentage of nulliparous women and those with only one pregnancy seems to reduce the importance of pregnancy as an etiological factor for cervical cancer. (Table V.) According to V. Fellenberg,[22] 33.2 per cent of women with cancer were nulliparous. Furthermore, it might be worthy of mention in this connection that the postulated excessive stimulation during pregnancy is unlikely due to estrogens. The greatest part, about 99 per cent, of estrogens during pregnancy are in the conjugated form of Estriol glucuronide, and thus in a physiologically inactive form.[23] Furthermore, cervical cancer is usually not associated with conditions due to excessive estrogen activity. On the other hand, the recent awareness of cervical cancer and its easier diagnosis have brought to light an unusually high incidence of cases during pregnancy. Whatever the reason for this not yet understood condition may be, it is, in the author's opinion, not caused by excessive estrogenic stimulation.

TABLE IV. AVERAGE NUMBER OF PREGNANCIES IN PATIENTS WITH CERVICAL CARCINOMA

	PREINVASIVE CANCER	INVASIVE CANCER
Premenopausal	2.0	2.6
Postmenopausal	2.8	5.8

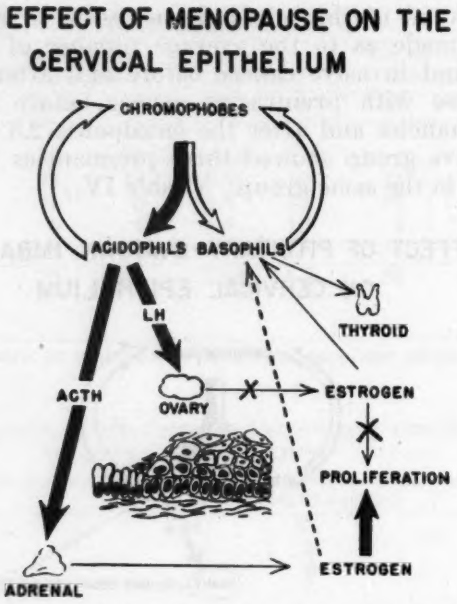

Fig. 4.—Continuous estrogenic stimulation to the cervix may occur following menopause by a different readjustment in the endocrine system.

Interval Between Last Pregnancy and Cancer.—Observations made on the time interval between the last pregnancy and diagnosis of cancer offer further evidence that pregnancy may not take the place in carcinogenesis as heretofore suggested. The shortest period found between the last pregnancy and diagnosis of preinvasive cancer is an average of ten years, and for invasive cancer, fourteen years in the premenopausal group, while the postmenopausal group shows for both preinvasive and invasive cancer an average of twenty-five years between the last pregnancy and cancer. (Table VI.) Out of 69 cases with preinvasive cancer reported by Pund,[24] 46 were diagnosed more than ten years after the last pregnancy.

TABLE V*

	PREINVASIVE CARCINOMA 100 CASES	INVASIVE CARCINOMA 100 CASES	
Nulliparous Patients With Cervical Carcinoma.—			
Premenopausal	21	10	
Postmenopausal	9	8	
Total	30	18	48, or 24%
Uniparous Patients With Cervical Carcinoma.—			
Premenopausal	25	30	
Postmenopausal	13	8	
Total	38	38	76, or 38%

*Note 62 per cent of patients with cervical carcinoma were nulliparous and uniparous women.

In the light of this evidence, it is difficult to understand how pregnancy may influence the development of cervical cancer. If it were true that the excessive hormone stimulation to the cervix during pregnancy is conducive to the genesis of cancer, the onset of cancer should certainly be closer to the last pregnancy.

TABLE VI. YEARS BETWEEN LAST PREGNANCY AND DIAGNOSIS OF CANCER (AVERAGE)

	PREINVASIVE CANCER	INVASIVE CANCER
Premenopausal	10	14
Postmenopausal	25	25

Conclusion and Summary

The observations made on 200 cases of invasive and preinvasive cervical cancer indicate that the commonly associated complaints are those of estrogen deficiency rather than increased estrogen activity. The equal incidence of cervical cancer in all age groups suggests that the genesis of cancer is not linked to the normal decline of estrogen activity after the menopause. In fact, 70 per cent of the postmenopausal women with preinvasive cancer fail to show the normally expected low estrogenic level.

The decreased estrogenic level before menopause and the relative increased activity after the menopause, apparently of prolonged duration without episodes of progesterone production, exert an excessive stimulation to the cervical epithelium. In addition, a primary decrease in the estrogenic level is usually accompanied by increased pituitary activity, and it is postulated that this increased release of a pituitary hormone together with the prolonged estrogenic action may be partly or wholly responsible for the morphogenetic changes in the cervical tissue eventually leading to cancer.

Experimental production of this condition in animals appeared to support this theory. Intrasplenic transplantation of ovarian and cervical issue produced prolonged estrogenic stimulation to the cervix, while the absence of estrogen in the circulation allowed an increase in pituitary activity which resulted in the development of a granulosa-cell tumor, and/or luteoma in the ovarian tissue and columnar cell proliferation with squamous metaplasia in the epithelium of the cervix similar to that seen in human beings.[25]

Similar changes in the cervical epithelium were produced by Hofbauer through intramuscular transplantation of bits of ox's anterior pituitary glands, or by repeated parenteral administrations of anterior pituitary extracts.[11] In recent years the role of the pituitary in tumorigenesis has been extensively demonstrated by various workers.[26-34]

The occurrence of cervical carcinoma at equal rates in all age groups up to the age of 60 indicates that its development is not linked to the transient changes in the endocrine system during the menopause. Our data suggest that the previously erroneous assumption of a greater incidence during certain age levels is due to the fact that most women who seek medical advice are at the age of 30 to 39 years and in the decade preceding menopause. Thus a greater number of cervical carcinomas were found in this age group.

There is a slight increase in preinvasive cancer past the age of 60 and a more marked rise in the incidence of invasive cancer in the older patients. The endocrine system, contrary to its condition during the childbearing age, is static in the postmenopausal period and not subject to cyclic changes. Since it appears that cervical cancer during the childbearing age is associated with an endocrine disorder which consists in the interruption of the cyclic balance and change to a continuous type of hormonal action, it may be conjectured that the postmenopausal period is more favorable for the development of an endocrine disorder which produces uninterrupted stimulation to the cervix.

The role of pregnancies in carcinogenesis of the cervix seems to be doubtful due to the large incidence in cancer patients of nulliparas, and those with one pregnancy only, and the long interval of ten to twenty-five years between the last pregnancy and the diagnosis of cancer.

These data and experimental findings are presented to draw attention to the association of cervical cancer with symptoms and conditions arising from or responsible for a protracted low estrogenic level.

Though at present the solution to preventive oncology in regard to cancer of the cervix consists in the routine screening of all women by exfoliative cytology, it is hoped that the pathogenesis of cervical cancer, and the associated disorders and symptoms described in this presentation may lead to more frequent diagnoses of cervical carcinoma in the subclinical stage.

References

1. Meyer, R.: Henke-Lubarsch' Hdb. Spez. Path. u. Hist. 7: 1, 162, Berlin, 1930, G. Springer.
2. Pund, E. R., and Nieburgs, H. E.: South. M. J. 43: 384, 1950.
3. Hofbauer, J.: Am. J. Obst. & Gynec. 25: 779, 1933.
4. Hofbauer, J.: J. Obst. & Gynaec. Brit. Emp. 46: 232, 1939.
5. Van Weering: Grossingen, 1933. (Abst. Ztschr. Krebsforsch. 14: 1, 1936.)
6. Allen, E., and Overholzer, M.: Surg., Gynec. & Obst. 9: 129, 1935.
7. Zuckerman, S.: Lancet 1: 435, 1937.
8. Hisaw, F. L., and Lendrum, F. C.: Endocrinology 20: 228, 1936.
9. Korenchewsky, V., and Hall, K.: J. Obst. & Gynaec. Brit. Emp. 14: 22, 1938.
10. Nieburgs, H. E., and Allen, L.: In preparation.
11. Hofbauer, J.: Am. J. Obst. & Gynec. 27: 633, 1934.
12. Rubinstein, B. B.: Endocrinology 27: 843, 1940.
13. MacDonald, A. M., and Robson, I. M.: J. Path. & Bact. 48: 95, 1939.
14. Salmon, N. G., Walter, R. J., and Geist, S. H.: Proc. Soc. Exper. Biol. & Med. 39: 467, 1939.
15. Pund, E. R., and Auerbach, S. H.: J. A. M. A. 131: 960, 1946.
16. Nieburgs, H. E., and Pund, E. R.: J. A. M. A. 142: 221, 1950.
17. Nieburgs, H. E.: In publication.
18. Glatthaar, E.: Personal communication.
19. Wespi, H. J.: Personal communication.
20. Nieburgs, H. E., and Pund, E. R.: In preparation.
21. Hofbauer, J.: Zentralbl. f. Gynäk. 55: 428, 1931.
22. V. Fellenberg, R.: Separatdruck aus dem Bull. Eidgenoss. Gesch. amtes 1940. N. 35.
23. Cohen, S. L., Marrian, G. F., and Watson, M.: Lancet 1: 674, 1935.
24. Pund, E. R., Nettles, J. B., Dick, F., and Cardwell, E. S.: South. M. J. 41: 711, 1948.
25. Nieburgs, H. E.: In preparation.
26. Narimatsu, C.: Jap. J. Obstet. 20: 397, 1937. (Abstr. Ztschr. f. Krebsforsch. 157, 1938.)
27. Biskind, M. S., and Biskind, G. R.: Proc. Soc. Exper. Biol. & Med. 55: 176, 1944.
28. Lipschutz, A.: Nature 157: 551, 1946.
29. Biskind, G. R., and Biskind, M. S.: Am. J. Clin. Path. 19: 501, 1949.
30. Evans, H. M., Simpson, M. E., and Li, C. H.: Growth 12: 15, 1946.

31. Li, M. H., and Gardner, W. U.: Science 105: 13, 1947.
32. Moon, H. D., Simpson, M. E., Li, C. H., and Evans, H. M.: Cancer Research 10: 297, 1950.
33. Moon, H. D., Simpson, M. E., Li, C. H., and Evans, H. M.: Cancer Research 10: 364, 1950.
34. Moon, H. D., Simpson, M. E., Li, C. H., and Evans, H. M.: Cancer Research 10: 549, 1950.

RESULTS OF AN EXPERIMENT IN THE CONTROL OF PELVIC CANCER*

CATHARINE MACFARLANE, M.D., F.A.C.S., MARGARET C. STURGIS, M.D., F.A.C.S., AND FAITH S. FETTERMAN, M.D., F.A.C.S., PHILADELPHIA, PA.

(From the Woman's Medical College of Pennsylvania)

EARLY in 1938, members of the Department of Gynecology at the Woman's Medical College of Pennsylvania undertook a clinical research to determine the value of periodic pelvic examination in the control of pelvic cancer. On Jan. 4, 1940, at a meeting of this Society, I had the honor to make a report on the first two years of this research. In June, 1944, a five-year report was made at a meeting of the American Medical Association in Chicago. In June, 1948, a ten-year report was made at another meeting of the same Association, also in Chicago. I appreciate this opportunity to acquaint the members of the Obstetrical Society of Philadelphia with the results of the research, to date.

During the year 1938 and the early part of 1939, Dr. Sturgis, Dr. Fetterman, and I succeeded in interesting in our experiment 1,319 white women, 30 to 80 years of age, presumably well. They secured the approval of their family physicians and agreed to come for pelvic examination twice a year for five years. At the end of the five-year period some of the volunteers felt that they had made their contribution to medical science and were not interested in continuing. Others, together with the examining physicians, were eager to continue for another five years. At the end of ten years, in 1948, a determined few decided to sign up for another five-year period or "For as long as we last," said one. This report will deal chiefly with a group of 666 volunteers who have continued for the thirteen-year period.

The research has received financial support from the American Medical Association, from the International Cancer Research Foundation, from the Pennsylvania and Philadelphia Divisions of the American Cancer Society, from the New York Medical Women's Association, and from private individuals. The cost has been approximately $2000.00 per year for secretarial service, statistical service, supplies, stationary, etc. The examining physicians gave their services. The examinees paid no fee.

Material

The examination consisted in a careful inspection of the vulva, a bimanual vaginal examination, a careful inspection of the cervix through a speculum, in a good light. At first we used Chrobak's probe test for friability of tissue, applied Lugol's solution to the cervix according to Schiller's technique, and recommended quite a few biopsies. As our familiarity with the appearance of the healthy cervix increased, our appreciation of the significance of deviations therefrom also increased. We became less inclined to recommend biopsies and

*Read at a regular meeting of the Philadelphia Obstetrical Society, Jan. 4, 1951.

more inclined to recommend the removal of diseased areas, erosions, etc., in toto, in order that a complete specimen might be submitted for microscopic examination. We did not use vaginal smears because we wished to keep the examination so simple that its results would be applicable to the practice of any physician at any crossroads of this country.

As reported at the meeting of this Society in 1940, three cancers of the uterine cervix and one cancer of the uterine body were discovered in the first examination of the 1,319 volunteers. The three cervical cancers were discovered in areas of papillary erosion. Two of these erosions had no appearance of malignancy. They were excised by the Sturndorf technique and sent to the laboratory. To our surprise, the report was "early squamous-cell carcinoma." The third erosion was large and roughly papillary. It did suggest the possibility of malignancy. This was confirmed by biopsy. The report being "squamous-cell carcinoma, relatively early." These three cancers were treated with radium. One was given 3,900 mg. hr. One was given 4,050 mg. hr. The third was given 4,800 mg. hr. The three volunteers were alive without evidence of recurrence in the fall of 1950, twelve years after the cancers had been discovered and treated.

The patient with cancer of the uterine body was handicapped medically so that operation could not be performed. Radium and x-ray were used. After six years the disease recurred. She died at the end of nine years.

No more pelvic cancers were discovered until 1942, when a fourth cancer of the cervix was discovered on the eleventh visit of Volunteer 527.

This patient was 64 years of age. In 1922, when 46 years of age, she had had a curettage, a cervical repair, and an intrauterine application of radium for menopausal bleeding. At that time, two small myomatous nodules were discovered at the internal os. In 1938, she joined the research group and came regularly twice a year. At her tenth visit, in September, 1942, she reported having noticed a spot of blood on one occasion. Examination showed a smooth, atrophic cervix which was somewhat congested and bled a little on examination. Her blood pressure was 210. In the absence of demonstrable pelvic pathology the "spot of blood" was attributed to arteriosclerosis and she was told to return if she noticed it again. Five months later, at her eleventh visit in February, 1943, she reported no bleeding and no discharge but examination revealed a smooth, red, polypoid growth protruding through the external os and looking for all the world like a Maraschino cherry. This bled on touch. The biopsy report was adenocarcinoma. Radium needles were inserted into the growth for 1,300 mg. hr. and 2,400 mg. hr. were given in the uterine cavity. The tortuous canal interfered with drainage. Pyometra developed. Adequate radium and x-ray treatment could not be given. The patient died with cancer in 1944.

In March, 1943, a myomatous uterus was removed from Volunteer 898 by supravaginal hysterectomy. The surgeon reported to us that a microscopic area of adenocarcinoma of the endometrium was discovered close to the incision across the cervix. This woman shows no evidence of recurrence after eight years.

In 1943, a lateral pelvic mass about the size of an orange was discovered on the ninth visit of Volunteer 186. At operation in a suburban hospital this was found to be a rapidly growing malignant tumor of the ovary with involvement of the peritoneum. The patient died within six months.

In 1945, just before she was due for her fifteenth visit, Volunteer 1037 noticed a tinge of blood on wiping the vulva. Upon examination, a growth about 0.5 cm. in diameter was found on the anterior vaginal wall about 2 cm. within the orifice. This bled on touch. Biopsy showed epidermoid carcinoma of the vagina. The growth was removed by cautery and radium was applied. The patient died with recurrence in the lungs after three months.

In 1949, a thickening of the anterior vaginal wall was discovered on the twenty-first visit of Volunteer 527. This proved to be carcinoma secondary to carcinoma of the

bladder. One of Philadelphia's distinguished urologists removed the bladder and implanted the ureters into the sigmoid. There is no evidence of recurrence after eighteen months.

In 1949, a carcinoma of the body of the uterus developed in Volunteer 565. She was a married woman 45 years of age who had been coming regularly twice a year for ten years. At her visit in December, 1949, she reported prolonged periods and vaginal discharge. Examination was negative. As these symptoms increased she reported to her family physician in February, 1950. He advised a curettage. The pathologist reported adenocarcinoma. A panhysterectomy was performed.

TABLE I. CANCERS FOUND, 1938-1951

Uterus—Cervix	4
Body	3
Vaginal wall	2
Ovary	1
Total	10

These ten cancers complete the list of pelvic cancers discovered during the thirteen-year period. No cancers of the vulva or Fallopian tube have developed so far. In addition to the cancers, 283 benign lesions of the pelvic organs were discovered in the continuing group of 666 volunteers. These include 202 inflammatory lesions of the cervix.

TABLE II. BENIGN LESIONS FOUND IN CONTINUING 666 VOLUNTEERS, 1938-1951

Inflammatory lesions of cervix	202
Myomatous tumors of uterus	39
Mucous polyps of cervix	30
Cystic tumors of ovary	7
Leucoplakic areas of cervix	2
Papillomas of cervix	2
Tuberculous ulcer of vagina	1
Total	283

In the first examination of the 1,319 volunteers, in addition to the four pelvic cancers, 236 inflammatory lesions of the cervix were discovered. These ranged from mild endocervicitis to extensive areas of papillary erosion. In subsequent examinations of the gradually diminishing group, an additional 293 inflammatory lesions were discovered. This makes a total of 529 inflammatory lesions discovered over the thirteen-year period. Of these, 239 were eliminated by appropriate methods. In the continuing group of 666 volunteers, 202 inflammatory lesions were recorded.

TABLE III. INFLAMMATORY LESIONS OF THE CERVIX IN CONTINUING GROUP OF 666 VOLUNTEERS, 1938-1951

Endocervicitis	17
Cervicitis	39
Cervicitis with erosion	
Simple	56
Follicular	17
Papillary	26
Non-specified	47
Total	202

As we became increasingly familiar with the appearance of the healthy cervix, we became convinced that these inflammatory lesions were no asset to the women. The fact that the three early cancers of the cervix discovered

on the first examination of the 1,319 volunteers occurred in areas of cervical erosion strengthened our opinion that inflammatory lesions of the cervix are areas in which cancer is prone to develop. We decided that instead of being watched or biopsied, the entire lesion should be removed by appropriate methods.

Results

This research does not lend itself to accurate statistical evaluation because of variations in the number of volunteers, their age, social state and parity. On the basis of the four pelvic cancers discovered in the first examination of the original 1,319 volunteers, the incidence of pelvic cancer could be stated as 0.3 per cent. On the basis of the ten pelvic cancers discovered during thirteen years in the continuing group of 666 volunteers, the incidence of pelvic cancer could be stated as 1.5 per cent.

The fact that four pelvic cancers and 236 inflammatory lesions of the cervix were discovered in the initial examination of 1,319 presumably well women is evidence of the value of these examinations. The fact that 6 additional pelvic cancers and 293 additional inflammatory lesions were discovered in subsequent examinations of a gradually diminishing group is evidence of the importance of repeated examinations. It is worthy of note that only one pelvic cancer was discovered in a single woman. This was the primary cancer of the anterior vaginal wall.

The time, effort, and expense involved in the discovery of ten pelvic cancers and 529 inflammatory lesions of the cervix was considerable. The examining physicians and the continuing volunteers believe this to have been worth while. Some time in the future, when the medical profession appreciates that it is as important to promote health as it is to cure disease, periodic pelvic examination will take its place as part of a periodic health examination. Until then, it will probably devolve upon gynecologists and a relatively small number of preventive medicine minded general practitioners to make these examinations. For a long time to come, it will be necessary to select for these examinations those women who appear to need them most. On the basis of our thirteen years' experience, we should give priority to married women thirty years of age and over. Single women should be informed of the significance of vaginal discharge, bleeding between periods or after the menopause, and of the need for consulting a physician if and when such symptoms occur.

At the beginning of the research Dr. Ludvig Hektoen, who sponsored the project in the Committee on Clinical Research of the American Medical Association, said, "It's chief value will probably be educational." Certainly, the volunteers and their friends have been educated as to the significance of the symptoms for which we inquire. Equally certainly, the examining physicians and perhaps some of their colleagues have been educated as to the value of regularly inspecting the cervix.

TABLE IV. SUMMARY OF RESULTS OF PERIODIC PELVIC EXAMINATION RESEARCH

Pelvic cancers discovered in first examination	4
Pelvic cancers discovered in later examinations	6
Total number of pelvic cancers discovered in thirteen years	10
Inflammatory lesions discovered in first examination	236
Inflammatory lesions discovered in later examinations	293
Total number of inflammatory lesions discovered in thirteen years	529
Total number of inflammatory lesions eliminated	239

It would have been interesting to have made routine vaginal smears in connection with these periodic pelvic examinations. In retrospect, it seems

possible that a vaginal smear taken on Volunteer 527 in September, when she reported a spot of blood, might have shown the presence of cancer five months before it was discovered at her next visit in February. It is possible that a smear taken on Volunteer 565 in December, 1949, when she reported vaginal discharge and prolonged periods, might have shown the presence of cancer cells before cancer of the body of the uterus was discovered by curettage in February, 1950.

Comment

The real test of the value of this experiment to control pelvic cancer lies in the number of cancers of the cervix discovered.

Three cancers of the cervix were discovered in the first examination of 1,319 presumably well women.

Only one additional cancer of the cervix was discovered in the gradually diminishing group of volunteers over a period of thirteen years.

This would seem to indicate that some cancers of the cervix may have been prevented by the discovery and elimination of 239 inflammatory lesions of the cervix as a result of the research.

136 South Sixteenth Street

Discussion

DR. MARY D. PETTIT.—It is a pleasure to have the opportunity to congratulate Dr. Macfarlane and her associates on the marvelous achievement in keeping 666 women coming every six months for 13 years. This study is a most interesting and educational one. The millennium will come, I imagine, when we are able to be assured that every patient who has a general physical examination will also have a pelvic examination included. There are numerous groups interested in promoting such examinations, including Dr. Blady's Cancer Committee and the Committee for the Study of Pelvic Cancer of the Philadelphia County Medical Society. Dr. Macfarlane's study has had a direct influence on the formation of these groups so important in stimulating preventive work. It occurs to me that we teachers must be failing somewhere, because after all why are not more pelvic examinations being done today? The members of this Society comprise a large number of the teachers in the city of Philadelphia. Possibly we should re-examine our teaching methods to insure that our students should carry over such a program into practice. They are failing in the essential thing of doing routine pelvic examinations. I am sure all of you have heard the story from patients that they went to their family doctor but no pelvic examination was made. This comes not only from well patients but also from patients who had definite symptoms. This group has a teaching responsibility to try to improve the practice of the next generation.

DR. LEWIS C. SCHEFFEY.—We really owe a debt of gratitude to these women upon whom these examinations have been made, and who would "stick it out as long as they live." Anyone interested in this subject knows that the patient is often her own worst enemy. In spite of our best follow-up efforts, we find we have to expend time and energy in getting back patients for periodical surveys. To go back 13 years, I well remember when Dr. Macfarlane talked this project over with members of this Society and she reminded me tonight of what had been said at that time. Dr. Cullen, for instance, had remarked that if your auto doesn't run you know when it is not working properly and needs attention and that applied to women as well, so why examine well women, except as an educational project? So two essential things have resulted: (1) The value of the pelvic examination in the apparently well person. I think that is the greatest accomplishment and Dr. Macfarlane's experiment has made more of us conscious of what we can find out in examining symptomless women. (2) I think, too, that proper teaching of medical students and graduates is most important in obtaining good results. In spite of Dr. Pettit's pessimistic remarks, I think that most teachers are saying to students with great

emphasis that the abnormal cervix is a liability. All that we have to do is look at the figures presented—almost 50 per cent of the abnormal cervical cases were taken care of properly. Removal of the diseased area and pathologic study of the tissue in entirety is a safety measure in preventing possible invasive or noninvasive lesions from developing. A word about the non-use of Papanicolaou smears in this study is in order. I think that it has been a good thing to have made this study without Papanicolaou smears, as it is an important control procedure. I am anxious to have these figures compared with Dr. Rakoff's figures from the Cytology Laboratory at Jefferson. You noticed too that Dr. Macfarlane said that the Schiller test was abandoned more and more as experience with observance of the normal cervix increased. The Schiller test does not tell you anything that the eye does not tell you; it merely indicates areas worthy of biopsy or removal. I thank you, Dr. Macfarlane for the privilege of being asked to discuss your paper and I can only add the commendation of the members of this Society for the excellent study that you and your associates have made, and which we all hope will go on for another 13 years at least.

DR. ROBERT W. HUNTER.—I wonder whether Dr. Macfarlane could tell us how she took her biopsies, was this an office procedure, or were the patients hospitalized? Were the biopsies sutured or was electrothermic desiccation used?

DR. THADDEUS MONTGOMERY.—This Society has been privileged in hearing a report on the widely recognized and highly regarded experiment of Dr. Macfarlane, Dr. Sturgis, and Dr. Fetterman in the control of pelvic cancer by periodic pelvic examination. I would like to join the other discussants in congratulating these workers not only upon the results in this latest release of findings, but also upon the entire project, the conception of which showed a high degree of imagination and forethought, and the conduct through these several years a very considerable amount of faithfulness and industry.

With the results that have been reported this evening there is little, if any, in which one can disagree. The entire undertaking has proved its premise to determine whether periodic pelvic examination can detect the presence of early cancer and provide for prompt therapy, and it has accomplished much of its major purpose in educating the laity and physicians upon the importance of measures of preventive medicine in this field.

To such a remarkable degree has this actually been done that the entire nature of gynecologic office practice has been transformed in the last decade. For those who have accepted the philosophy of preventive gynecology the semiannual and annual examinations have become 50 per cent or more of the content of office practice. Much of the remainder of the time is involved in the clearing up of minor lesions which might be cancer disposing and the adjustment of functional disturbances. In fact, so rapidly does this phase of practice increase that it becomes increasingly a problem to find space for new patients who come with positive complaints or known organic disturbances.

As time goes on, it is to be hoped that the major portion of these reproductive tract check-ups can be done by the general practitioner as a part of periodic health examination. However, at the present time, for one or more of several reasons, the gynecologist may have to carry this burden of this part of the periodic study.

In addition to these widely accepted observations this paper emphasizes several of the points which are frequently noted in the studies of the Philadelphia Committee on Pelvic Cancer: for instance,

1. The importance of even minor degrees of genital spotting or bleeding.

2. The fact that what appears to be a simple erosion of the cervix may be early cancer.

3. That the ordinary methods of diagnosis, including inspection, palpation, diagnostic dilatation and curettage, and biopsy, are still the most important considerations in diagnosis.

(Parenthetically, I may say at this point that after four years of extensive use of Papanicolaou smears in office practice I have not yet encountered a case where the smear

revealed the diagnosis of pelvic cancer independently of dilatation and curettage and biopsy.)

4. The necessity for adequate radiologic or surgical therapy in the treatment of cervical and uterine carcinoma.

5. The difficulties in establishing an early enough diagnosis of ovarian cancer.

The essayists have laid considerable emphasis upon the possible significance of inflammatory lesions of the cervix in the etiology of cervical carcinoma, and have found it advisable to excise the entire lesion both as a method of treatment and as specimen for multiple histologic section. While there is still some difference of opinion as to the significance of laceration and erosion in cancer etiology, most of us would agree that the clearing up of such lesions may prove a very important factor either in avoidance of cancer or in eradication of small foci; and that there is probably no more definite way of getting rid of diseased areas than by complete excision. To one who practices obstetrics and sees patients in the early years of life with small areas of erosion either before or after delivery, this method of handling seems a trifle radical. In the patient in the early age group Papanicolaou smear, biopsy, and coagulation would seem adequate. In middle life, and particularly after childbearing is completed, then certainly amputation of the cervix or electrothermic resection is preferable.

One would like to agree with the statement that the excision of local cervical lesions reduced the number of carcinomas of the cervix which appeared in those 666 women who persisted with periodic examination up to the present time. I suspect, however, that there are other factors that would have to be ruled out before this statement could be accepted on its face value. One of them I can think of, which I have experienced in my own private practice, is the fact that the Jewish patient who is least susceptible to cervical carcinoma accepts intellectually the value of periodic health examination and is the most faithful in carrying out her part in this program. I wonder, for instance, what percentage of these 666 patients who persisted with the study might have been of this category.

The statement is also made that only one single woman developed cancer of the genital tract and this did not involve the cervix. However, nothing was said about the total number of single women who were studied.

Finally, while we are discussing the general topic of periodic health examination from the gynecologist's standpoint, it might be well to remind ourselves at this time that carcinoma of the breast is more frequent among women than carcinoma of both the cervix and uterus combined, and the periodic physical examination offers the doctor an excellent opportunity to check up on breast pathology and instruct the patient in methods of breast examination as well as to determine the state of the pelvic organs.

I know that Dr. Macfarlane and her colleagues are in sympathy with this point of view and have avoided mentioning it simply because of their very correct decision to confine their paper to matters of pelvic cancer.

DR. MACFARLANE (Closing).—Beginning with Dr. Hunter's question, I do not like to take biopsies but prefer to remove the entire unhealthy area by knife or conization. In the case of a small, discrete lesion, I prefer excision in the operating room where facilities for the control of bleeding are available, if it occurs.

Dr. Montgomery pointed out that our statistics require further study as to social state, race, age, etc. If and when our group becomes static, it will be possible to do this.

Dr. Klingensmith's suggestion that our pathologic specimens might be reviewed with reference to the presence of pre-invasive cancer is good. I hope that this will be done. Taking vaginal smears would have been interesting.

I was glad to hear Dr. Pettit speak of improved teaching methods and hope this includes regular assignment of students to cancer detection clinics where, in their impressionable years, they may learn the techniques and the value of these examinations.

ABDOMINAL MYOMECTOMY, ADVANTAGES AND DISADVANTAGES*

EQUINN W. MUNNELL, M.D., AND FREDERICK W. MARTIN, JR., M.D.,
NEW YORK, N. Y.

(From the Sloane Hospital for Women [Presbyterian] and the Department of Obstetrics and Gynecology of the College of Physicians and Surgeons)

WHEN the fibroid uterus is to be operated upon, the usual surgical procedure chosen is hysterectomy. Not only is conservative myomectomy much less commonly employed, but also, at the Sloane Hospital for Women at least, the relative frequency of this operation since 1932 has actually decreased. In 1932, 14 per cent of the fibroid uteri operated on were treated by myomectomy, but in 1949 only 8 per cent received conservative treatment. Fig. 1 illustrates the great increase in hysterectomies for fibroids during this period with the relatively slight rise in number of myomectomies.

When gynecologic surgeons are asked why the radical procedure of hysterectomy is preferred to myomectomy, a number of reasons will be given. These include age, increased morbidity, failure to relieve symptoms, possibility of recurrence of fibroids which may or may not necessitate further surgery, technical impossibility or difficulty, and patients' wishes. There is no doubt that most of these factors are problems to be considered, but that they are always carefully considered and weighed against the importance of continued fertility is doubtful. Substance is given to this doubt by the completely reversed ratio of ward to private patients in so far as myomectomy and hysterectomy are concerned in the cases to be discussed. Sixty-five per cent of all hysterectomies for fibroids between 1942 and 1949 were performed on *ward* patients, while 64 per cent of all myomectomies during these years were done on *private* patients. Some of this discrepancy, but not all, can be explained by the much higher incidence of salpingitis in the ward patients. Other explanations are that the private patient presents herself with smaller tumors or that she is more articulate than her ward sister in making known her desire to retain her uterus.

I. Material Studied

This includes 370 ward and private myomectomies performed at the Sloane Hospital for Women between 1932 and 1947, a fifteen-year period. Excluded from this number were all vaginal myomectomies and those abdominal myomectomies considered incidental and not significant to the operation, thus leaving a working remainder of 236 "significant" abdominal myomectomies.

A. Color.—Eighty per cent of the myomectomies were performed on white women and 20 per cent on Negro women.

B. Age.—The average age at time of myomectomy was 33.2 years with the youngest patient being 21 years and three patients being over 50 years. The age distribution is shown in Fig. 2.

*Presented at a meeting of the New York Obstetrical Society, Jan. 9, 1951.

II. The Advantage of Myomectomy—Continued Fertility

Although there are some patients for whom continued menstruation has psychological importance, the only indication for myomectomy worthy of general consideration is the preservation of fertility.

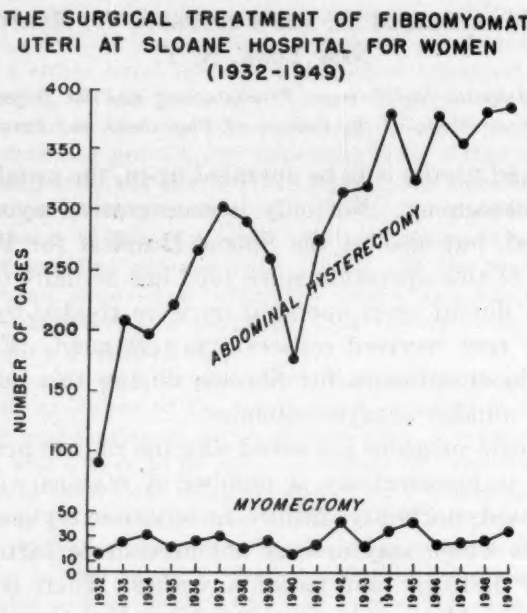

Fig. 1.

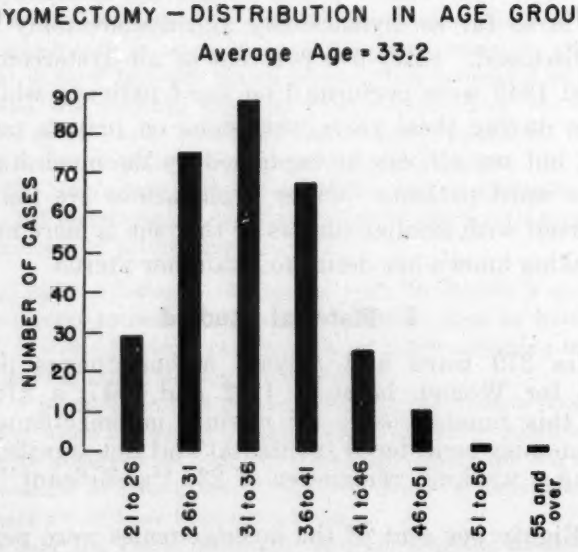

Fig. 2.

A. Subsequent Pregnancies.—Seventy, or 30 per cent, of the 236 patients with abdominal myomectomies subsequently became pregnant, 16 of these women having previously borne viable offspring. As shown in Table I, 9 of these 70

aborted after becoming pregnant and had no subsequent term pregnancies, but 61 patients, or 26 per cent, went on to one or more successful term pregnancies. We know of a total of 81 successful term pregnancies, 14 spontaneous abortions, 1 ectopic, and 1 hydatidiform mole.

TABLE I. PREGNANCIES AFTER MYOMECTOMY

A. Patients subsequently becoming pregnant	70	(30%)
B. Had abortions only	9	
C. Had term pregnancies	61	(26%)
D. Total known pregnancies	97	
E. Total term pregnancies	81	
F. Spontaneous abortions*	14	
Tubal pregnancy	1	
Hydatidiform mole	1	

*Includes B.

Fifty per cent of Frank's patients with myomectomies subsequently became pregnant, 40 per cent of Mussey's, 38 per cent of Bonney's, 35 per cent of Counseller's, 36.5 per cent of Miller's, 31 per cent of Ahltorp's, and 23 per cent of Finn's (Table II*). In general, these authors and others feel that the value of subsequent pregnancies justifies myomectomy in selected cases in women in the childbearing age.

Eleven, or 20 per cent, of our patients having subsequent successful pregnancies were over 35 years at the time of myomectomy, the oldest being 42 years.

TABLE II. SOME COMPARATIVE RESULTS FOLLOWING MYOMECTOMY

	SUBSEQUENT PREGNANCIES (%)	RELIEF OF STERILITY (%)	RECURRENCE OF FIBROIDS (%)	REOPERATION REQUIRED (%)
Frank	50			
Mussey and associates	40			
Bonney	38			
Counseller and Bedard	35		20.0	
Ahltorp	31	24	24.8	5
Miller	37			3
Finn and Muller	23	32	23	12
Munnell and Martin	26	47	21	12

B. Method of Delivery Following Myomectomy.—Table III summarizes the method of delivery of the first term pregnancy after myomectomy. Pregnancies following hysterotomy or cesarean section and myomectomy are not included. The high cesarean section rate for the group as a whole, 17.6 per cent, is explained by the following: First, there is the addition of another possible indication for cesarean, namely, previous myomectomy; second, the history of previous myomectomy will, in a large number of cases, lead the obstetrician to consider the other indications for section in a more liberal light. Even so, this figure of 17.6 per cent cesarean section rate is one-half that of Bonney's 33 per cent.

Seven per cent of the first term deliveries were delivered by cesarean section because of a history of previous myomectomy, a figure identical with that of Finn and Muller's who reported 5 sections because of previous myomectomy in 64 term deliveries. Ahltorp reports an incidence of 1 in 24, or 4 per cent.

*In Table II we have summarized some comparative results of other authors with regard to subsequent pregnancies, relief of sterility, recurrence of fibroids, and reoperation after myomectomy.

1. Factors determining method of delivery after myomectomy: The first, and most important factor, is that of infection of the uterine scar during the postoperative course. This was the indication for cesarean section in 2 cases. Emphasizing the importance of this factor, one of these 2 patients was found to have a silent rupture of the uterus at time of elective section.

The second factor determining method of delivery is the extent of the myomectomy incision, particularly as to its depth or relation to the uterine cavity. One of the two patients in our series who became pregnant following myomectomy in whom the uterine cavity was entered was delivered by elective cesarean section, no endometrium being found at the site of the myomectomy scar. Ahltorp's series suggests that this factor of extent of the myomectomy incision is actually of little importance in the matter of subsequent delivery; he reports 5 patients becoming pregnant following myomectomy during which the uterine cavity was entered, all being safely delivered by the vaginal route, 4 spontaneously and 1 by low forceps. Phaneuf feels that cesarean section is a safer method of delivery if the fibroid uterus was submucous and if there had been considerable invasion of the uterine cavity.

TABLE III. METHOD OF DELIVERY OF FIRST TERM PREGNANCY AFTER MYOMECTOMY

	VAGINAL DELIVERY	CESAREAN SECTION BECAUSE OF PREVIOUS MYOMECTOMY	CESAREAN SECTION FOR OTHER REASONS	METHOD OF DELIVERY UNKNOWN
Myomectomy incision not close to uterine cavity	39	1*	5	1
Myomectomy incision very close to uterine cavity	1	2†	0	0
Myomectomy incision entered uterine cavity	0	1‡	0	1
Totals	40	4 (7%) (17.6%)	5	2

*Stormy postmyomectomy course, 15 cm. intramural fibroid.
†One of these had a "silent" rupture of uterus.
‡No endometrium found at site of previous myomectomy.

2. Danger of rupture of the uterus: Miller states that there is no need to fear rupture of the postmyomectomy pregnant uterus during labor. Ahltorp considers rupture of the pregnant uterus an infrequent occurrence following myomectomy, citing 20 cases of rupture in 1,300 pregnancies after myomectomy reported in the literature, an incidence of 1.5 per cent. Hurd's case is included in Ahltorp's report. Finn and Muller report one. Meredith reports 3 silent ruptures of the uterus following myomectomy, all being discovered at time of elective section. There was one silent rupture in our own series, details of which are here presented:

Patient L. F. (Unit No. 496311) was a white woman, 29 years old, gravida 0. The past history was irrelevant. The chief complaints were menorrhagia and dysmenorrhea. In 1936, dilatation and curettage, myomectomy, and left oophorectomy (chocolate cyst) were performed. A 10 cm., submucous, intramural fibroid was removed with considerable difficulty, dissection being carried down to but not through the endometrium. She became very sick postoperatively, developing a *Staphylococcus aureus* septicemia, pneumonia, wound infection, and possibly a pyometra. She recovered with complete relief of symptoms. Subsequently, she married and became pregnant, being delivered in 1942 by elective low-flap cesarean section because of the history of myomectomy. At operation a defect was found in the uterine wall through which the membranes were visible. Adhesions were extensive.

Mother and baby both did well. Nineteen months later a second elective cesarean section was performed successfully at which time Pomeroy sterilization was done. The patient is living and well in 1950.

In commenting on the rarity of rupture of the pregnant uterus following myomectomy in contrast to the frequency of rupture after cesarean section, Greenhill offers three reasons for this difference. First, there is no interference with wound healing in the nonpregnant uterus which is at rest while the puerperal uterus continues to undergo contractions. Second, there is no bacterial invasion of the nonpregnant uterus while bacterial invasion of the cesarean scar is frequent. Third, fewer and smaller sutures are necessary to control bleeding in the nonpregnant uterus, thus minimizing necrosis from excessive suture pressure.

Examination of our own material plus Ahltorp's interesting figures would suggest that vaginal delivery can be anticipated following myomectomy unless there is evidence that the uterine scar was weakened as a result of postoperative infection. Extent of myomectomy is of much less importance as an indication for cesarean section.

C. Myomectomy During Pregnancy.—Child and Douglas and Mussey and associates call attention to the high fetal loss when myomectomy is done during pregnancy and advise against it except for extremely urgent reasons. As shown in Table IV, our own series includes 19 cases of myomectomy during pregnancy, the period of gestation at time of operation ranging from a few weeks to 6 months. Pregnancy continued successfully to term in only 5 of the 19. Eight patients aborted postoperatively, and the uterus was unavoidably entered during myomectomy in another 6 patients, thus necessitating removal at that time of the gestational products. Thus, there was a 74 per

TABLE IV. MYOMECTOMY DURING PREGNANCY

CASE NO.	AGE	DURATION OF PREGNANCY	REASON FOR SURGERY	FIBROIDS REMOVED			OUTCOME
				NO.	SIZE (CM.)	LOCATION	
1	32	3 mo.	Large myoma	1	11	SS	Went to term
2	28	4 mo.	Painful degeneration	1	12	SS	Aborted 3 wk. later
30	37	4 mo.	?	1	4	SS	Hysterotomy
37	25	4½ mo.	Painful degeneration	2	16	IM	Hysterotomy
54	34	"Early"	Wrong diagnosis	4	1-7	SS IM	Hysterotomy
77	32	3 mo.	Degeneration	1	7	IM	Hysterotomy
97	24	2½ mo.	?	1	9	IM	Hysterotomy
102	24	7 wk.	Ovarian cysts	2	6 11	SS	Went to term
147	?	5 mo.	Painful degeneration	1	11	IM	Aborted same day
160	32	6 mo.	Painful degeneration	1	15	SS	Went to term
165	31	4½ mo.	Painful degeneration	8	1-10	SS IM	Aborted ten days later
186	25	3½ mo.	Painful degeneration	7	1-16	SS IM	Hysterotomy
191	38	6 mo.	Painful degeneration	3	1-5-15	SS	Went to term
209	34	5 mo.	Painful degeneration	1	?	SS	Aborted 3 days later
213	37	9 wk.	Painful degeneration	3	3	SS	Aborted 3 days later
233	28	8 wk.	Painful degeneration	1	9	SS	Aborted
235	27	8 wk.	Painful degeneration	1	10	SS	Went to term
236	36	10 wk.	Painful degeneration	5	1-8	SS IM	Aborted
126a	21	8 wk.	Painful degeneration	2	2-3	SS	Aborted 28 days later
		SUMMARY:	Total cases			19	
			Went to term			5	
			Aborted or hysterotomy			14 (74%)	

cent fetal loss when myomectomy was performed during pregnancy. Where abortion did not occur, the removed fibroids were all subserous. Myomectomy during pregnancy is a highly undesirable procedure.

D. Myomectomy and Sterility.—Table V summarizes the results of myomectomy in 30 patients complaining of sterility. Seven patients with adnexal disease were excluded when calculating the degree of successful results. Of the remaining 23, 13 were known to become pregnant, 11 (47 per cent) having successful term pregnancies for a known total of 18 successful births. Uterine suspension was also performed in 5 patients, but myomectomy was considered the only significant aspect of the operation. It would appear, therefore, that myomectomy has a definite place in the treatment of certain cases of sterility.

The oldest successful patient in this sterility group was 42 years at time of myomectomy and one-quarter were over 36 years.

Finn reports 32 per cent success in his series and Ahltorp 24 per cent where myomectomy was done for sterility.

TABLE V. STERILITY AND MYOMECTOMY

A. Total sterility patients having myomectomy		30	
B. Associated adnexal disease		7	
Pyosalpinx	1		
Hydrosalpinx	1		
Tubes closed	2		
Endometriosis	1		
Parovarian cyst (both became pregnant)	2		
C. Determinate remainder (A minus B) (i.e. no organic cause for sterility other than myoma)		23	
D. Patients with subsequent term pregnancies		11	(47%)
E. Patients with abortions only		2	
F. Total term pregnancies		18 in 11 patients	
G. Age at myomectomy			
	Term Pregnancies	*Failures*	
26-30	5	7	
31-35	4	7	
36-40	3	3	
42	1		

E. Myomectomy and Habitual Abortion.—This was a small group, statistically not significant, yet interesting (see Table VI). There was a total of 9 patients with a history of 2 or ore spontaneous abortions; 6 of these had had

TABLE VI. HABITUAL ABORTION AND MYOMECTOMY

A. Patients with history of three or more spontaneous abortions	6
1. Subsequently went to term	3
2. Total known term pregnancies (minimum)	5
3. No follow-up	1
B. Patients having had only two abortions before myomectomy	3
1. Subsequently went to term	2
2. Total known term pregnancies	3
3. No follow-up	1

3 or more miscarriages. One-half of the patients in the true habitual abortion group subsequently went to term, as did 2 of the 3 with only 2 previous abortions. These results also suggest that myomectomy may be indicated in the treatment of habitual abortion, particularly if the myoma is intramural in location as was the case in all but one of the successful cases in this series.

III. Relief of Symptoms

As outlined in Table VII, it will be seen that 93 per cent of the patients obtained complete or partial relief of symptoms. Pain was the easiest symptom to relieve and bleeding next. Fair results were obtained in the patients in the dysmenorrhea group, some of whom had simultaneous uterine suspension without significant effect on the results.

TABLE VII. RELIEF OF SYMPTOMS AFTER MYOMECTOMY IN 97 PATIENTS WITH AVAILABLE HISTORY AND FOLLOW-UP

	CURED	IMPROVED	NO RELIEF
Bleeding	27 (66%)	11 (27%)	3 (7%)
Pain	27 (84%)	5 (16%)	0
Dysmenorrhea	12 (50%)	8 (33%)	4 (17%)
Over-all	66 (68%)	24 (25%)	7 (7%)

IV. Disadvantage of Myomectomy—Reappearance of Fibroids

Unfortunately, myomectomy is not always a final procedure, since preserving the uterus may mean retaining invisible seedling fibroids which may subsequently increase in size and cause symptoms, or new tumors may form in this organ which is so prone to develop neoplasms.

Counseller had a 20 per cent recurrence rate. Ahltorp reports a recurrence rate of 24.8 per cent of which one-fifth required reoperation for hysterectomy. Finn and Muller report a 23 per cent recurrence with one-half of these patients requiring reoperation (Table II). Our own results are presented in Table VIII, and we have included in the reoperation rate those patients subsequently receiving radiation castration as well as those having later hysterectomy. Fibroids reappeared in at least 49 patients, an incidence of 21 per cent. Twenty-three patients required subsequent hysterectomy for fibroids, and one patient subsequently required hysterectomy for endometrial polyp and cystic and glandular hyperplasia. Following myomectomy four patients required radiation castration for recurrent fibroids and one patient for benign bleeding. The minimum reoperation rate, therefore, was 12.3 per cent.

TABLE VIII. THE RECURRENCE OF FIBROIDS AND SUBSEQUENT UTERINE OPERATIONS FOLLOWING 236 SIGNIFICANT MYOMECTOMIES

A. Total known recurrences	49	
"Minimum" recurrence rate		21%
B. Total known subsequent hysterectomies	24	
For fibroids 23 (3 of these at time of cesarean section)		
For polyp and hyperplasia 1		
C. Total known subsequent radiation castrations	5	
For fibroids 4		
For benign bleeding 1		
D. "Minimum" reoperation rate (B plus C) ÷ 236		12.3%
E. Total interval pregnancies where fibroids recurred—		
26 in 20 patients		
Successful—22 in 16 patients		
Abortions—4 in 4 patients		
F. Average age at time of myomectomy	32.4	
Over 35 at time of myomectomy 7 (14%)		

Perhaps balancing this 21 per cent recurrence rate and 12.3 per cent reoperation rate is the fact that about 40 per cent of the patients with recurrent fibroids had further pregnancies after myomectomy and before recurrence of the tumors. At least 22 successful term births occurred in this group of 49 patients whose fibroids later reappeared.

The average age at time of enucleation in this group with recurrences was 32.4 years with an age distribution range of 23 to 40 years. Fibroids reappeared in only 14 per cent of the women who were over 35 years at time of myomectomy. Recurrence is less likely in the older patients because there is a shorter period of time to the menopause with its physiologic shrinkage of existing fibroids and prevention of new fibroid growth.

Thirty-seven and one-half per cent of the recurrences were in Negro women, although this race made up only 20 per cent of the entire series.

No malignant gynecological tumors developed in any of the patients in this series.

V. Other Factors

A. Mortality (Immediate).—There was only one postoperative death in this series, and it cannot be attributed to the fact that myomectomy was performed in preference to hysterectomy. This patient was 47 years old when she was operated on for a large, subvesical fibroid which was removed with great difficulty. Hysterectomy would have been more difficult. Death resulted on the third postoperative day from peritonitis and ileus resulting from a perforated bladder.

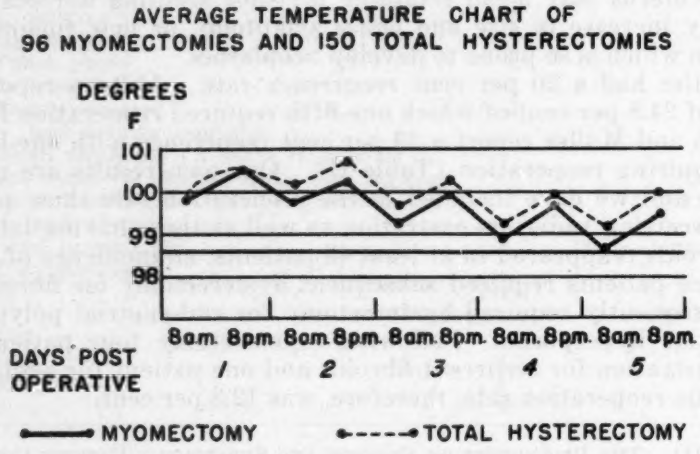

Fig. 3.

B. Morbidity.—A composite temperature chart of the 8 A.M. and 8 P.M. temperatures of 97 patients who had myomectomy with or without uterine suspension or dilatation and curettage is shown in Fig. 3. It compares favorably with a similar temperature chart for hysterectomy (Munnell).

C. Postoperative Complications.—As seen in Table IX, these were not inconsiderable, although only the patient with the *Staphylococcus aureus* septicemia came close to dying. Thus 9, or 3.8 per cent, of the myomectomy patients had relatively serious postoperative complications. However, this incidence is no higher than it would be for a similar series of total hysterectomies (Munnell). In addition, there were less serious complications consisting of 4 wound infections and 2 urinary tract infections.

D. Sequelae.—Subsequent intestinal obstruction took place some years later in 2 patients, one of whom died as a direct result.

Case 76 was a 37-year-old white woman who had had two large myomas removed in 1936. Two years later, she developed acute intestinal obstruction. At laparotomy, a confused mass of intestines was found adherent to the uterus. Enterostomy was performed. The patient died three days later.

Case 179 was a 31-year-old Negro woman with a history of three spontaneous abortions followed by five years of sterility and menorrhagia. She had three small intramural fibroids removed in 1943. Appendectomy was performed at the same time. Four years later, she developed intestinal obstruction due to a fibrous band between the abdominal incision and upper sacrum, necessitating resection of a gangrenous loop of bowel. She recovered and subsequently had two elective cesarean sections for cephalopelvic disproportion.

TABLE IX. POSTOPERATIVE COMPLICATIONS FOLLOWING 236 OPERATIONS FOR MYOMECTOMY

Paralytic ileus (moderate to severe)	3
Wound disruption	1
"Stormy" postoperative course (fever, distention)	1
Staphylococcus aureus septicemia, pneumonia, wound infection, pyometra	1
Thrombophlebitis	1
Pulmonary embolus (both mild; both on twentieth postoperative day)	2

Thus, intestinal obstruction due to adhesions of the small bowel to the myomectomy site or abdominal incision, while an infrequent occurrence, nevertheless constitutes a dangerous sequel to myomectomy. Careful closure of the uterine serosa and avoidance of too large or too many serosal incisions should be important technical considerations at the time of myomectomy.

VI. Comment

We come then to the auditing of the myomectomy account. Do the assets of the operation, that is, a 26 per cent chance of having future successful pregnancies, outweigh the liabilities? The liabilities are a 21 per cent chance of recurrence of fibroids and at least a 12 per cent chance of requiring subsequent hysterectomy or radiation castration. The mortality rate, degree of morbidity, and frequency and severity of postoperative complications are no higher than those of hysterectomy. Chances of relief of symptoms are excellent. Given these odds, there can be little doubt that most women in the childbearing age with no children, or perhaps only one child, would gladly choose myomectomy in preference to hysterectomy. With these same odds and the desire of the patient to maintain the childbearing capacity, the gynecologist should give more consideration to the possibility of myomectomy when dealing with the fibroid uterus than he now does.

What should be the age limit for myomectomy? Our own series suggests the maximum to be 42 years, but Bonney revised his earlier estimate of the age limit from 41 up to 46 years. First pregnancies in the mid-forties, while uncommon, are certainly not rare, and perhaps Bonney's figure is justified in some cases.

In the last analysis the selection of myomectomy in preference to hysterectomy depends entirely upon the obstetrical history and future childbearing desires of the individual patient in any age group. There would be no point in performing myomectomy in a woman in her latter thirties who had two or more children and no desire for a larger family. However, a woman at almost any premenopausal age who desires children should not be denied myomectomy when it is technically feasible. The technical difficulties of myomectomy are undoubtedly frequently exaggerated, as evidenced by Bonney's 1937 report of 632 myomectomies in which he was deterred, as he says, neither by size, position, nor number of fibroids. Bonney has been further quoted as saying

that "since cure without deformity or loss of function must ever be surgery's highest ideal, the general proposition that myomectomy is a greater surgical achievement than hysterectomy is incontestable."

VII. Summary and Conclusions

1. Myomectomy is now an infrequently performed operation.

2. A series of 236 "significant" abdominal myomectomies is analyzed.

3. Twenty-six per cent of these myomectomy patients subsequently had successful pregnancies. The oldest patient to become pregnant was 42 years at time of enucleation.

4. Vaginal delivery without increased obstetrical risk can be anticipated in the great majority of patients becoming pregnant after myomectomy. Cesarean section should be elected in that occasional patient in whom there is an infection of the myomectomy incision. In addition, some authorities feel that a deep, extensive myomectomy incision is an indication for elective cesarean section.

5. Myomectomy during pregnancy should be avoided if possible since it causes a high fetal loss by abortion.

6. Myomectomy is indicated in the treatment of sterility and habitual abortion if other factors involved are normal.

7. Good relief of symptoms is obtained after myomectomy.

8. The disadvantage of myomectomy is a minimum recurrence rate of 21 per cent and a minimum reoperation rate of 12 per cent.

9. Morbidity, mortality, and postoperative complications compare favorably with the same following hysterectomy.

10. The maximum age limit for myomectomy is at least 42 years.

11. Myomectomy is the desirable surgical treatment for fibromyomata uteri in women in the childbearing age desiring subsequent pregnancies and should be more frequently elected. It is completely justified by the value of preservation of fertility.

References

1. Hurd, R. A.: Am. J. Obst. & Gynec. **26**: 889, 1933.
2. Bonney, V.: J. Obst. & Gynaec. Brit. Emp. **44**: 1, 1937.
3. Counseller, V. S., and Bedard, R. E.: J. A. M. A. **111**: 675-679, 1938.
4. Greenhill, J. P.: Editor's Comment, 1938 Yearbook of Obstetrics and Gynecology, Chicago, Yearbook Publishers, p. 357.
5. Miller, H. E.: Tri-State M. J. **13**: 2664, 1941.
6. Phaneuf, L. E.: Surg., Gynec. & Obst. **79**: 182-191, 1944.
7. Child, C. G., III, and Douglas, R. G.: Am. J. Obst. & Gynec. **47**: 213-228, 1944.
8. Mussey, R. D., Randall, L. M., and Doyle, L. W.: Am. J. Obst. & Gynec. **49**: 508, 1945.
9. Ahltorp, G.: Acta obst. et gynec. Scandinav. **26**: Suppl. 6, 1946.
10. Munnell, E. W.: Am. J. Obst. & Gynec. **54**: 31-39, 1947.
11. Ross, J. W.: Am. J. Obst. & Gynec. **53**: 266-270, 1947.
12. Louros, N. C.: J. Obst. & Gynaec. Brit. Emp. **55**: 635-641, 1948.
13. Frank, R. T.: J. A. M. A. **140**: 1001-1008, 1949.
14. Finn, W. F., and Muller, P. F.: Am. J. Obst. & Gynec. **60**: 109-116, 1950.
15. Meredith, R. S.: Personal communication.

622 West 168th Street.

Discussion

DR. M. A. GOLDBERGER, New York, N. Y.—Dr. Munnell has presented a very interesting subject. There are many hospitals in the city and in other parts of the country that

are loathe to do myomectomy as an operation of choice. They prefer hysterectomy. Our group at Mount Sinai Hospital has been doing myomectomy wherever it could be done in women of childbearing age. I think Dr. Munnell's paper bears out many points I would stress. A paper is now being prepared by Dr. Arthur Davids. He has collected over 1,000 cases of myomectomy. It is very interesting to note that from 1920 to 1933, 281 myomectomies were done with 8 deaths in that series. From 1935 to 1950, 765 myomectomies were done with 1 death. That death was in a woman of 32 years with a very large three-month size myoma who did very well for five days and had a fatal pulmonary embolus and died. Our percentage of pregnancies has been pretty near that which Dr. Munnell reported, between 40 and 50 per cent. We now feel that the reason for our better results and lower morbidity in myomectomy has been an improvement in technique, that is, planning the original incision so that the maximum number of myomectomies can be done through that incision. Dr. Rubin first used in our hospital a tourniquet to control hemorrhage during the operation. It is a rubber catheter placed through two holes in the broad ligament and around the uterine vessels and held taut with a clamp. One can leave this tourniquet on for as long as ten minutes and operate in a bloodless field. The use of fine catgut for suturing and hemostasis is stressed. Blood should always be available. The use of antibiotics is another factor in lower morbidity and better results. In addition, early ambulation is encouraged.

Some men say their reason for doing hysterectomy as against a myomectomy is because it is technically easier.

The size of the uterus or number of fibroids does not deter us from doing this operation.

I agree with Dr. Munnell in his conclusions, but I would stress that myomectomy should be more seriously considered by gynecologists.

DR. THOMAS PEIGHTAL, New York, N. Y.—I am pleased that Dr. Munnell has chosen to re-emphasize the importance of myomectomy as a sound surgical procedure in the handling of fibroids. Formerly, when endocrine therapy was less effective in controlling symptoms subsequent to hysterectomy, nearly all gynecologists did myomectomy at almost any age up to the fourth decade, but today hysterectomy is usually done, particularly in cases of multiple fibroids with excessive bleeding, except in those cases where the desire for pregnancy is the prime consideration. The increased use of hysterectomy in recent years has been due also to the high incidence of recurrence (21 per cent in Dr. Munnell's series) and to the usually low percentage of successful pregnancies after myomectomy. Dr. Munnell is to be congratulated on his 35 per cent subsequent pregnancies. His low mortality is noteworthy. The chief complication following myomectomy is postoperative ileus due to plastic adhesion of small intestinal loops to uterine suture lines. Some of us have used sheets of allantoic membrane to form a smooth hood over the fundus after extensive myomectomy in an attempt to prevent adhesions. This has lowered the occurrence of ileus in our patients, but one must always be on the lookout for this complication and be prepared to reoperate promptly once mechanical ileus is recognized. Finally, we agree with Dr. Munnell that the technical difficulty of doing extensive myomectomy is often exaggerated, for it is our belief that this operation can be done on every patient where it is regarded as the procedure of choice, particularly if one uses the scheme of controlling general hemorrhage by injecting 1 or 2 c.c. of Pituitrin into the fundal musculature before making the multiple myomectomy incisions.

DR. HARVEY MATTHEWS, Brooklyn, N. Y.—I agree with practically everything Dr. Munnell has said. It will be noted that the discussers so far have been gynecologists who have limited their discussions to the surgery of myomectomy. I should like to call attention to the obstetrical side of the problem. Any competent surgeon can do a good myomectomy. With proper technique there is nothing to fear from the surgical standpoint. On the other hand, when the patient is likely to become pregnant, the obstetrical problem becomes most important. I have not been able to make up my mind which patient, following myomectomy, to deliver per vagina and upon which to perform elective cesarean section. This is a difficult question and a very important one to mother and baby. If the endometrial cavity is not entered; if hemostasis is complete; if closure of the myomectomy wound is carefully per-

formed; and if no infection develops, vaginal delivery may be accomplished successfully. However, who knows which incision can be trusted to withstand the strain of normal labor and delivery, to say nothing of a prolonged complicated one? Therefore, I would again call attention to the importance of myomectomy during the childbearing age. The danger of rupture of the myomectomy scar during labor far outweighs, in my opinion, the surgical risk of performing elective cesarean section.

DR. GORDON DOUGLAS, New York, N. Y.—Most of Dr. Munnell's figures indicate a striking similarity between his material and that of Dr. Finn and Dr. Muller in their analysis of the cases from our service in the New York Lying-In Hospital.

To the best of my knowledge there has been only one patient admitted to the New York Lying-In Hospital since 1892 with a ruptured uterus following a previous myomectomy. Two publications from this institution on the subject of rupture of the uterus appeared in the *Transactions of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons,* the first in 1908 and the second in 1926. I have personally reviewed all cases of rupture of the uterus in this institution since that time. Only one instance of rupture of the uterus following myomectomy in such a vast clinical material would appear to answer the question concerning its frequency that was raised this evening. I believe this material is in agreement with the experience in Bellevue Hospital and the Margaret Hague Maternity Hospital.

I heartily endorse what Dr. Peightal had to say concerning the use of the intrauterine injection of Pitocin at the time of operation.

DR. MUNNELL (Closing).—Louros experienced the same progressive lowering of the operative mortality rate in myomectomy that Dr. Goldberger has mentioned to be the experience at Mount Sinai Hospital. Louros reports a progressive lowering of operative mortality from 10 per cent in his first 100 myomectomies to 1 per cent in his fourth 100 myomectomies, attributing this decline to improvement in operative technique. As mentioned by Dr. Bullard, the eminent British gynecologist Victor Bonney was always a strong supporter of the conservative operation of myomectomy and carried his conservative surgery into the management of ovarian cysts and tumors as well, since he felt that ovarian neoplasms like the simple serous cyst and dermoid cysts could often be resected.

The sterility results in our series are much higher than those in reports of other institutions, and it may well be that this is simply due to statistical accident since the number of cases involved is not large.

I think that Dr. Matthews speaks for the majority of American gynecologists when he intimates some apprehension on allowing a woman to go through labor and vaginal delivery after she has had a myomectomy in which the incision entered the uterine cavity extensively. I myself would have the same apprehension under these conditions. However, the report of Ahltorp and the writings of others suggest very strongly that rupture of the uterus following myomectomy is extremely uncommon. Incidently, Ahltorp has written a very lengthy and authoritative monograph on myomectomy.

EXCHANGE RESINS AND TOXEMIA OF PREGNANCY*

A Preliminary Study

L. D. ODELL, M.D., G. A. JANSSEN, M.D., J. C. NOVELLI, B.A., AND D. G. RALSTON, M.S., OMAHA, NEB.

(From the Department of Obstetrics and Gynecology, the University of Nebraska College of Medicine)

EDEMA in obstetric patients is usually treated by a restriction of sodium chloride (NaCl) in the diet. Various adjuncts, however, have been used to aid in the elimination of water and NaCl from the body. These include hypertonic glucose, ammonium chloride, and other diuretic agents. It is noteworthy that sodium is eliminated through the kidney with these substances although the mechanism varies in each case. The advent of exchange resins for managing edema offers a new approach since sodium is eliminated through the intestine bound to the exchanger.

Most ion exchangers are synthetic resins or zeolites which may be converted to acids by carboxyllation. The amount of sodium removed by resins varies according to the dosage, the sodium chloride intake, the patient, and the type of resin employed. Resins have an affinity for all electrolytes but because sodium is ten times as abundant in body fluids the uptake is mostly in that substance. However, to safeguard against the escape of potassium from the cells, an addition of potassium may be made to the resin preparation. Studies were undertaken to evaluate the use of a cation exchange resin with added potassium on women with excessive weight gain and on women with edema associated with toxemia of pregnancy. In addition, other studies were made and reported.

Material and Method

Patients were obtained from the obstetric service of the hospital. Except in designated instances, they were admitted to the hospital for study because of an excessive weight gain (usually over thirty pounds) or because of preeclampsia. In the hospital, accurate records were obtained of their weight, intake and output, and change in clinical status. Resin was administered by mixing 10 Gm. of carboxyllated resin and 5 Gm. of potassium resin with 200 ml. of water. This mixture, after being stirred vigorously, was given three times daily. Carbon dioxide content and combining power were determined on a Van Slyke apparatus. Urine protein was determined quantitatively.[1] Sodium was measured in the urine as chloride.[2] Although the chloride method leaves much to be desired and tends to lessen the definitiveness of our results, technical difficulties made it impossible to measure sodium as sodium in either the urine or feces at the present time. Among other studies made were: Pituitrin test,[3]

*Supported by a grant from Eli Lilly & Company, Indianapolis, Ind., who likewise supplied the preparations used in this study.

cold pressor test,[4] tetraethyl ammonium chloride floor (TEAC floor),[5] Sodium Amytal* test and serum B-glucuronidase activity.[6] In regard to the last of these, the digest was inactivated by adding trichloracetic acid after the glycine buffer (but before adding sodium hydroxide) in order to eliminate the objection of precipitated proteins carrying down free phenolphthalein and diminishing the intensity of the color.[7] Diets were calculated according to the established standard of Bills and associates[8] at 2,000 calories.

Results

The effect of resin administered to four nonhospitalized normal patients on a regular prenatal diet (6, 7, 32, and 33 weeks pregnant) is listed in Table I. No depression in the CO_2 content of venous blood occurred over a three-week

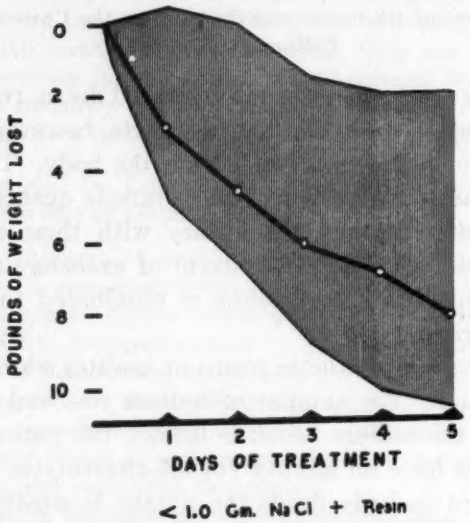

Fig. 1.—Graph represents variation and mean weight loss in pounds of ten patients treated with resin and less than 1-Gm. NaCl diet.

period of treatment. The normal rate of weight gain was unaffected and untoward subjective symptoms occurred in only one patient. A fifth normal patient (37 weeks pregnant) was treated for three weeks, during which time the CO_2 combining power dropped from 46.4 volumes per cent to 36.8 volumes per cent during the third week of therapy.

Ten hospitalized patients (Fig. 1) admitted for excessive weight gain (including three with pre-eclampsia) were placed on a 1-Gm. NaCl diet with resin. An average weight loss of 8.0 pounds occurred over a five-day period of treatment. During this time the CO_2 combining power dropped an average of 7.3 volumes per cent. No untoward symptoms were observed. Blood calcium levels were unchanged by therapy.

Ten hospitalized patients (Fig. 2) admitted for excessive weight gain including one with pre-eclampsia, were placed on a 3-Gm. NaCl diet with resin. An average weight loss of 7.8 pounds occurred over a five-day period of treatment. A similar depression occurred in CO_2 combining power. No untoward symptoms were observed. It is noteworthy that a 13.5 pound weight loss occurred in one patient suffering from pre-eclampsia (Fig. 5).

*Sodium Amytal test. In the evening blood pressures are obtained at 15-minute intervals. Sodium Amytal 0.03 Gm. is administered every half hour for three doses or until the patient falls asleep. The sleeping blood pressure is considered basal. The test is measured as the difference between the systolic and diastolic pressures of the control and basal pressures.

In view of the compensated acidoses, chlorides were being partly secreted by other means (in combination with ammonium ion) and sodium must have escaped by a separate route (intestine). No depression was observed in urea clearance during therapy. One patient (Fig. 5) treated with resin had a renal depression presumably from pre-eclampsia. In this case, an elevated blood nonprotein nitrogen (NPN) precipitated the decision for delivery. Blood pressure and proteinuria were not adversely affected by resin therapy. Other findings are listed in the following case reports and figures.

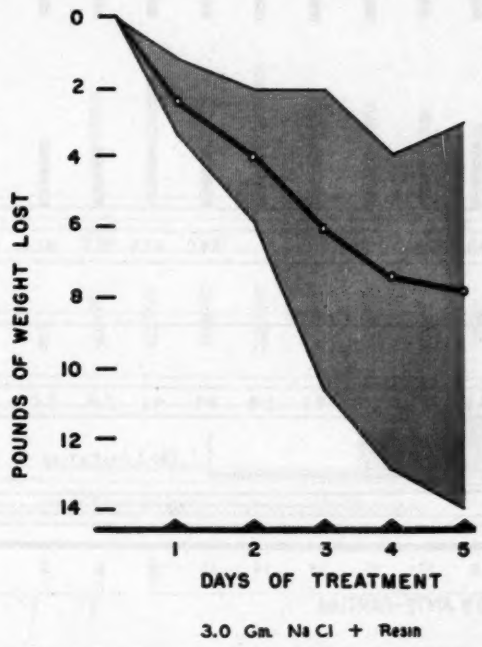

Fig. 2.—Graph represents variation and mean weight loss in pounds of ten patients treated with resin and a 3-Gm. NaCl diet.

Case 1.—B. W. (No. 103941) aged 18 years, white, para 0, gravida i, estimated date of confinement Oct. 26, 1950, was admitted for study Sept. 21, 1950, with a 28-pound weight gain. Examination disclosed a near-term pregnancy, one plus edema, a blood pressure of 135/90 mm. Hg and a slight proteinuria. There were no subjective symptoms. On a 1-Gm. NaCl diet and resin, a 10-pound weight loss occurred over a five-day period. The patient was discharged on Sept. 26, 1950, on resin therapy but with no salt restriction. During the ensuing 13 days, the patient regained weight rapidly (159 to 176 pounds), returning on Oct. 9, 1950, in active labor. At that time the blood pressure was 130/90, edema two plus, proteinuria four plus. Shortly after admission the blood pressure rose to 180/120 accompanied by a frontal headache, epigastric pain, and edema of the face and hands. Sodium Amytal, 50 per cent magnesium sulfate intramuscularly, and chloral hydrate controlled the toxemia and the patient was delivered after a nineteen-hour labor under pudental block anesthesia of a living female infant weighing 5 pounds, 7 ounces. In the immediate postpartum period the blood pressure was controlled with sedatives and the urine output established with intravenous 20 per cent glucose. The blood pressure returned to normal and the urine cleared before discharge. At six weeks the blood pressure was 115/80 and the urine protein less than 0.1 Gm. in a twenty-four-hour specimen. Findings of ophthalmoscopic examination shortly after delivery were compatible with pre-eclampsia (vessel spasm). The packed cell volume was 50 per cent at delivery (hemoconcentration). The urea clearance on the fifth

day postpartum was 72 per cent of normal. Other findings are portrayed graphically and are listed in Fig. 3. From this case it is evident that a limitation of dietary NaCl is necessary if resin therapy is to be effective for curbing abnormal water retention.

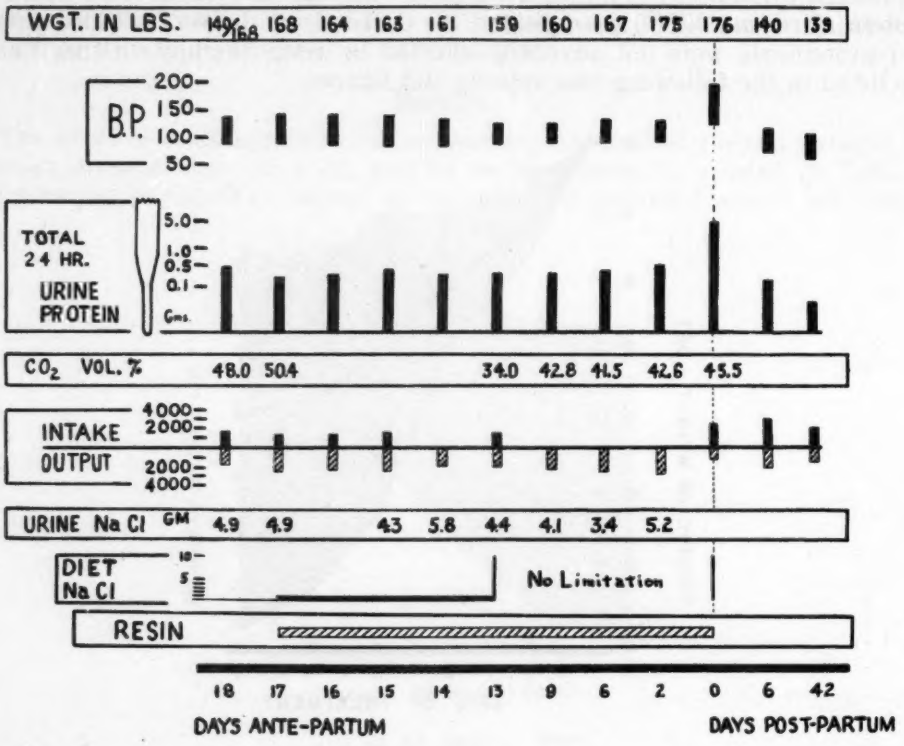

Fig. 3.—From 140 to 168 pounds represents reported weight gain during pregnancy. The patient was discharged from the hospital on resin but with no NaCl limitation to diet. B-glucuronidase activity in serum was 1,900 units.

Case 2.—L. C. (No. 104088) aged 29 years, para ii, gravida iii, estimated date of confinement Jan. 15, 1951, was admitted on Oct. 21, 1950, for toxemia of pregnancy. There was no previous history of hypertension. The patient had gained 15 pounds during pregnancy. Examination disclosed blood pressure of 190/115 mm. Hg, one plus edema, four plus proteinuria. The patient complained of a severe throbbing frontal headache of twenty-four hours' duration and epigastric pain. The blood pressure and urine had been normal one week previously. The uterine height (MacDonald) was 23 cm. Under observation the patient lost 10 pounds of weight over a five-day period on a 1-Gm. NaCl diet and resin therapy. On the fourth antepartum day resin therapy was discontinued and the NaCl intake was increased to 15 Gm. daily by adding supplementary tablets of enteric-coated NaCl. Fetal heart tones could not be detected after Oct. 30, 1950, and on Oct. 31, 1950, the patient was delivered under saddle block anesthesia of a 2 pound, 3 ounce, dead male infant after a labor of one hour and thirty minutes. Ophthalmoscopic examination the day of admission disclosed transient arteriolar spasm but no permanent vascular damage and on the fourth antepartum day no pathology was noted. The patient was discharged on the sixth postpartum day with blood pressure of 130/70 and a slight proteinuria. Examination six weeks later disclosed normal blood pressure and urine. A urea clearance test on the eighth antepartum day was 107 per cent of normal, plasma proteins 6.96 Gm. per cent and uric acid 3.9 mg. per cent. Additional findings are listed and graphically portrayed in Fig. 4. In this patient the cessation of resin

therapy and substitution of a 15-Gm. NaCl diet did not result in a significant return of edema or increase in weight. It is noteworthy that the pressor response to Pituitrin diminished after the loss of edema (weight).

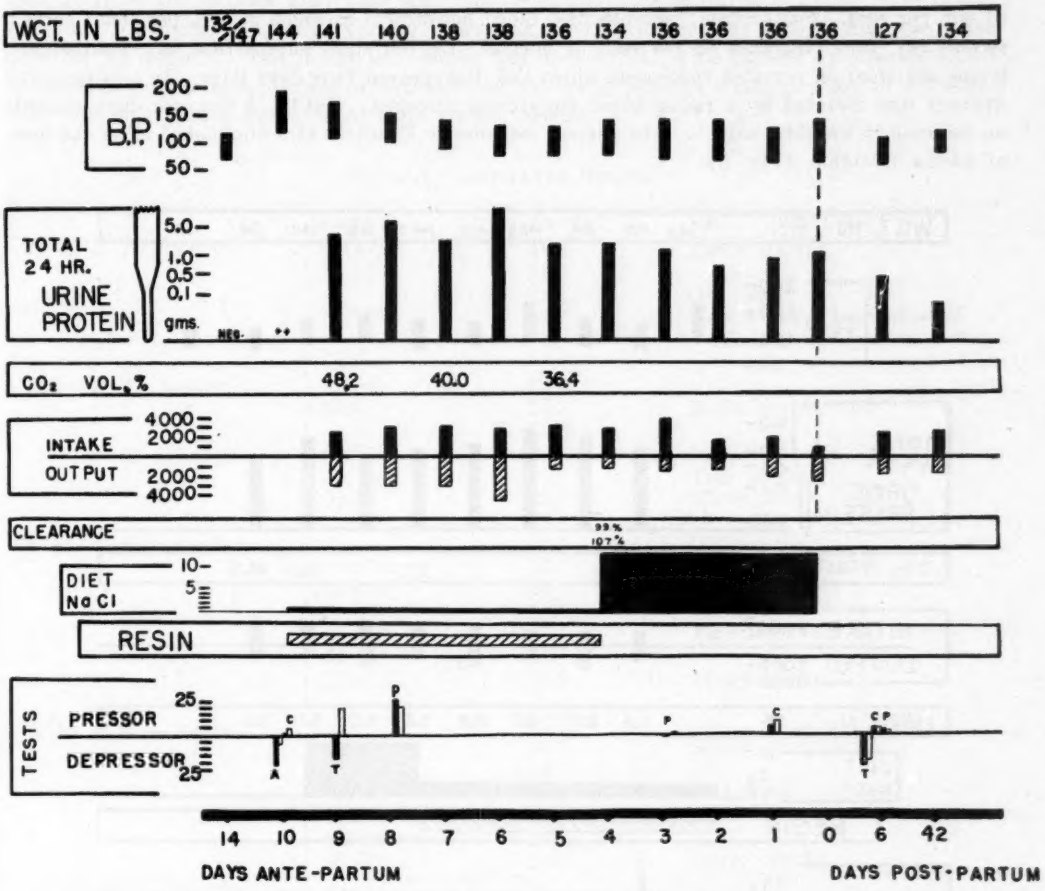
WGT. IN LBS. 132 147 144 141 140 138 138 136 134 136 136 136 136 127 134
B.P. 200 150 100 50
TOTAL 24 HR. URINE PROTEIN 5.0 1.0 0.5 0.1 gms. NEG. ++
CO2 VOL. % 48.2 40.0 36.4
INTAKE 4000 2000
OUTPUT 2000 4000
CLEARANCE 99% 107%
DIET NaCl 10 5
RESIN
TESTS
PRESSOR 25
DEPRESSOR 25
C P A T
14 10 9 8 7 6 5 4 3 2 1 0 6 42
DAYS ANTE-PARTUM
DAYS POST-PARTUM

Fig. 4.—From 132 to 147 pounds represents reported weight gain during pregnancy. Note that weight did not increase following administration of 15 Gm. NaCl per day. A, Depression in systolic (closed bar) and diastolic (open bar) pressures during Sodium Amytal test; C, rise in systolic and diastolic pressures with ice-water test; T, change in systolic and diastolic pressures with administration of 400 mg. of tetraethyl ammonium chloride intravenously (TEAC floor); P, rise in systolic and diastolic pressures with Pituitrin. Note that pressor response to Pituitrin diminished after the loss of weight (water). B-glucuronidase activity in serum was 1,042 units.

Case 3.—I. W. (No. 104732) aged 19 years, para 0, gravida i, estimated date of confinement Feb. 3, 1951, was admitted on Dec. 11, 1950, for toxemia of pregnancy. The patient was unmarried and had no prenatal care. A 32-pound weight gain had occurred. Examination disclosed a blood pressure of 170/100 mm. Hg, two plus edema, and a two plus proteinuria. The patient complained of a moderate frontal headache of one week's duration. The height of the fundus was 23.5 cm. (MacDonald). Under observation the patient lost 13.5 pounds over a five-day period on a 3-Gm. NaCl diet and resin. On Dec. 16, 1950 (second antepartum day), resin therapy was discontinued and the NaCl intake increased to 15 Gm. per day with supplementary tablets. The weight increased from 146.5 to 150 pounds within two days. Delivery was facilitated on Dec. 18, 1950, by elective cesarean section and a 3 pound, ½ ounce, male infant was delivered who survived. The blood pressure and urine analysis returned to normal before discharge on the seventh postpartum day. Six weeks after delivery the blood

pressure and urine were normal. Other chemical findings were as follows: *Antepartum:* sixth day, blood nonprotein nitrogen 33.8 mg. per cent, total serum protein 5.71 Gm. per cent; fourth day, urea clearance 60 per cent of normal; second day, urea clearance 66 per cent of normal, blood uric acid 5.35 mg. per cent; day of delivery, blood nonprotein nitrogen (NPN) 61 mg. per cent. *Postpartum:* seventh day, blood nonprotein nitrogen 30 mg. per cent; forty-second day, urea clearance 69 per cent of normal. On the sixth antepartum day, ophthalmoscopic examination revealed vasospasm which had disappeared four days later. In this patient, delivery was dictated by a rising blood nonprotein nitrogen. NaCl (15 Gm. per day) caused an increase in weight (water). The pressor response to Pituitrin also diminished after the loss of edema (weight) (Fig. 5).

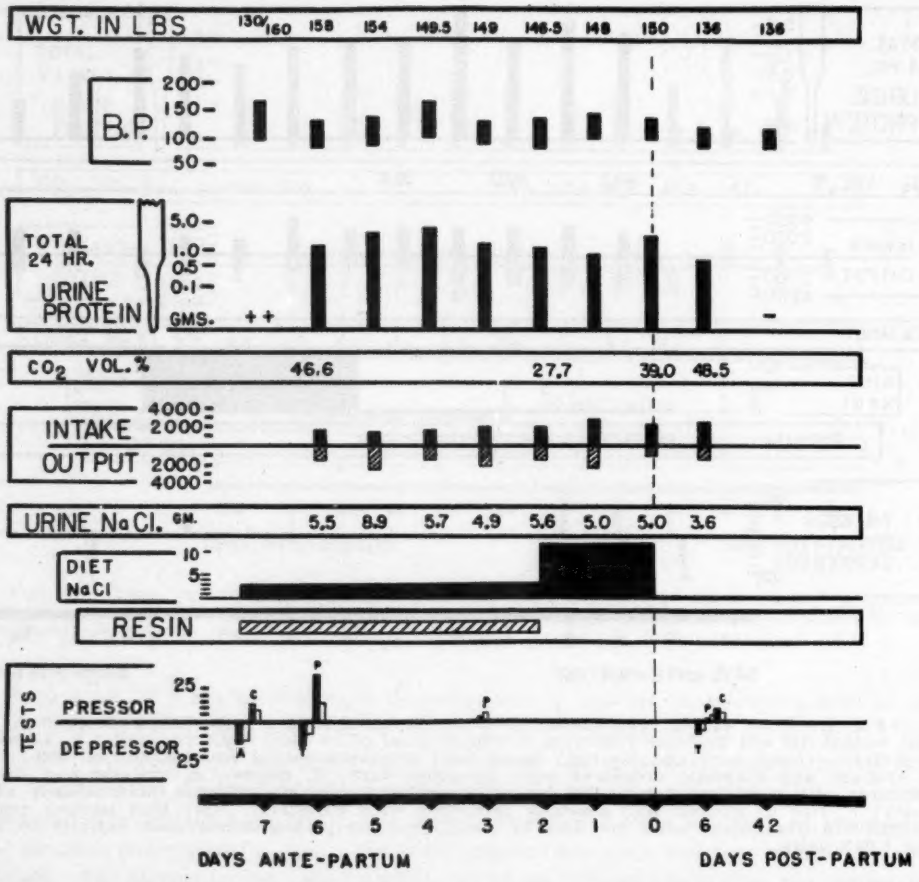

Fig. 5.—From 130 to 160 pounds represents reported weight gain during pregnancy. Note that weight increased rapidly following administration of 15 Gm. NaCl per day. A, Sodium Amytal test; C, ice-water test (cold pressor); T, TEAC floor; P, Pituitrin test. Note that pressor response to Pituitrin diminished after the loss of weight (water). B-glucuronidase activity in serum was 2,000 units.

CASE 4.—In a fourth case the reverse of the observed phenomena of desensitization to Pituitrin was elicited. This patient, a 19-year-old, white nulligravida, was admitted near term for a 32-pound weight gain but with no other toxemic findings. After five days a 6-pound weight loss occurred on a 3-Gm. NaCl diet and resin. Resin was discontinued and the NaCl intake was increased to 15 Gm. per day. At that time the Pituitrin test was 6 mm. systolic and 14 diastolic. In three days 3 pounds were gained and the blood pressure rose from 120/80 to 155/110. On the third day the patient complained of a frontal headache. The Pituitrin test was 24 systolic and 22 diastolic. The urine disclosed no increase in protein

per twenty-four hours but the amount had decreased to 500 ml. in the preceding twenty-four hours. Because of these findings the NaCl intake was decreased to 3 Gm. whereupon the blood pressure returned to normal and all subjective symptoms disappeared. Two days later, Jan. 2, 1951, the patient went into labor spontaneously and delivered a living male infant weighing 7 pounds, 4 ounces. During labor, the blood pressure was 135/90 and the urine negative for protein. The subsequent course was uneventful. This patient apparently failed to adapt to the increased intake of sodium chloride. It is believed a continuation of a 15-Gm. NaCl diet might have precipitated more serious results.

TABLE I. EXCHANGE RESINS

	WEIGHT*	CO_2 CONTENT	REMARKS
Case 1 (6 weeks)	56.885	21.8	Resin started
	55.035	21.5	
		21.1	One week
	56.770	22.7	Two weeks. Discontinued because of dyspnea
Case 2 (7 weeks)	52.645	22.9	
	52.495	24.5	Resin commenced
		23.6	
	52.610	25.7	One week
	53.502	24.6	Two weeks
	53.150	25.2	Three weeks
Case 3 (32 weeks)		26.4	
	56.900	27.1	Resin commenced
	56.400	25.4	One week
	54.940	27.3	
	57.220		Two weeks
	57.560	27.7	
	57.870	26.0	Three weeks
Case 4 (33 weeks)		27.3	
	61.850	25.5	Resin commenced
	61.740	24.7	
	62.740	24.5	One week
	62.270	23.0	Two weeks
	62.530	24.5	
	63.305	26.2	Three weeks

*Weights in kilograms, obtained on a beam balance scale.

Comment

The hazards of exchange resins have been reviewed by Dock and Frank.[9] Among the reported undesirable effects are: gastrointestinal irritation, acidosis, and depletion of potassium and calcium. In the present study, a compensated acidosis was the only untoward effect observed. The addition of potassium resin probably served to prevent depletion of that ion from the cells. The exchange resins used in these experiments are difficult to put into solution because of the surface tension of the particles. Outpatients will quite naturally complain of having to drink the suspension since it tastes not unlike suspended sand. However, the advent of a newer "sodium removing resin"* has partially overcome this objection since it dissolves more readily and is more palatable.

It has been demonstrated that the efficiency of resins for removing sodium is better at a higher NaCl intake.[9] Favorable clinical results from resin have been demonstrated on edematous cardiac patients and on patients with hepatic cirrhosis by Martz and co-workers.[10] It was our observation that the clinical effect (weight loss) was practically as satisfactory on a 3-Gm. NaCl diet (7.8

*Sodium-removing resin, Eli Lilly & Company, Indianapolis, Ind.

pounds) as on a 1-Gm. NaCl diet (8.0 pounds). It is significant that a 3-Gm. NaCl diet is of practical value in instructing outpatient cases on a low-salt diet. However, several points regarding the use of exchange resins in pregnant patients with edema need further clarification. The recent addition of a flame photometer to our laboratory will enable us to measure the sodium uptake in the feces and, in addition, to measure more accurately the urine and blood electrolytes. Likewise, the dosage of resin, much like the dosage of insulin, may have to be adjusted for each patient. In addition, further experiments with diets should be conducted so that the optimum amount of NaCl intake can be determined.

Some mention should be made of our experience with various tests designed to identify pre-eclampsia. We have been unable to find a single proposed test which is either specific or of prognostic value. It may be suggested that whenever a test fails to identify pre-eclampsia the disease is of another sort (latent hypertensive disease, nephritis, etc.). We believe this to be wishful thinking since none of these diagnoses (pre-eclampsia, latent hypertension, and nephritis) can be specifically identified clinically or chemically in all patients. The results of our studies with various tests for pre-eclampsia are being presented separately.[11] To our knowledge the desensitization to solution of posterior pituitary (Pituitrin test)[3] after loss of edema (weight) is the first such reported observation. The explanation of this phenomenon presents several interesting possibilities which are beyond the scope of this paper.

Summary

Carboxyllated resin and potassium resin administered to pregnant patients near term with excessive weight gain and with pre-eclampsia resulted in an average weight loss of 8.0 pounds in ten patients on a 1-Gm. NaCl intake and in an avearge weight loss of 7.8 pounds in ten patients on a 3-Gm. NaCl intake. Resin therapy caused a compensated acidosis. In one patient resin therapy was associated with a consistantly depressed urea clearance test and with a rising blood nonprotein nitrogen. Loss of weight (water) is associated with a lessened pressor response to solution of posterior pituitary.

References

1. Shevky, M. C., and Stafford, D. D.: Arch. Int. Med. **32**: 222, 1923.
2. Hawk, P. B., Bergeim, O., Oser, B. L., and Cole, A. G.: Practical Physiological Chemistry, ed. 11, Philadelphia, 1937, P. Blakiston's Son & Co.
3. Dieckmann, W. J., and Michel, H. L.: Am. J. Obst. & Gynec. **33**: 131, 1937.
4. Dieckmann, W. J., Michel, H. L., and Woodruff, M.: Am. J. Obst. & Gynec. **36**: 408, 1938.
5. Brust, A, A., Assali, N. S., and Ferris, E. B.: J. Clin. Investigation **27**: 717, 1948.
6. Odell, L. D., and MacDonald, D. F.: Am. J. Obst. & Gynec. **56**: 74, 1948.
7. Lorincz, A., Novelli, J. C., McGoogan, L. S., and Odell, L. D.: Am. J. Obst. & Gynec. **61**: 527, 1951.
8. Bills, C. E., McDonald, F. G., Niedermeic, William, and Schwartz, M. C.: J. Am. Dietetic A. **25**: 304, 1949.
9. Dock, W., and Frank, N. R.: Am. Heart J. **40**: 638, 1950.
10. Martz, B. L., Kohlstaedt, K. G., and Helmer, O. M.: J. Lab. & Clin. Med. **36**: 962, 1950.
11. McIntire, R. J., Odell, L. D., and Novelli, J. C.: In preparation.

FETAL TRAUMA FROM FORCEPS DELIVERY

T. Stacy Lloyd, Jr., M.D., Simon V. Ward, M.D., F.A.C.S., and Thomas Benton Sellers, M.D., F.A.C.S., New Orleans, La.

(From the Southern Baptist Hospital)

THIS is an analysis of 456 unselected cases at the Southern Baptist Hospital, New Orleans, La., in which forceps were employed in vaginal deliveries on babies in the vertex presentation. The study refers specifically to the incidence and types of marks on the fetal head from the use of forceps in the second stage of labor. We have not attempted, however, to study the effect of forceps on the maternal soft parts. A search of the literature for the past thirty-five years fails to reveal a similar study.

We were prompted to make this survey not only in the hope of lowering the incidence of forceps trauma to the fetus by a study of the relative dangers of the various types of forceps, but also to provide a statistical analysis, lacking in the literature, of such trauma. It is at times embarrassing to be questioned by a mother regarding marks on the baby's head. More often than not, the mother believes a forceps delivery to be a very radical procedure indeed, not understanding the major role which the use of forceps plays in modern normal obstetrics.

This study is not intended to compare the relative skill of specialists and general practitioners, but to compare the results of the use of various types of forceps in the hands of these groups of accoucheurs.

Methods

Following each vertex vaginal delivery in which forceps were employed, the baby was inspected with respect to severity and location of forceps marks. These babies were inspected initially, before being carried from the delivery unit, and later in the nursery for any delayed effects of forceps trauma. Each delivery was classified regarding (1) the operator: whether a member of the house staff, general visiting staff, or obstetrical staff (the latter consisting of those who limit their practice to obstetrics and gynecology); (2) type of forceps; (3) station of the fetal head when forceps operation was begun; (4) position of fetal head on delivery; (5) purpose of forceps (whether for extraction or rotation plus extraction); and (6) location and severity of forceps marks. The "marks" were noted to be indentations, contusions, excoriations, cuts, or any combinations of these.

Our classification of station is that defined by the American Committee on Maternal Welfare: "The relationship of the largest diameter or circumference of the presenting part to the plane of least dimensions which passes through the ischial spines."[1]

Findings

General Considerations.—For the first six months of 1950 the incidence of the use of forceps in all vertex vaginal deliveries in the 456 deliveries of the

present series was 58.3 per cent, which compares closely with Kamperman's study.[2] Excluding the necessity of individualizing cases with respect to the need for forceps, several factors play roles in accounting for this incidence:

1. The practice of many of our staff of following De Lee's dictum of "prophylactic low forceps" whenever possible.
2. The desire to shorten the second stage of labor for whatever indication.
3. Teaching purposes.

During this time, the obstetric staff handled 72 per cent of the vertex vaginal deliveries, the general staff 20 per cent, and the house staff 8 per cent. The obstetric staff handled 68 per cent of the primiparous vaginal deliveries, employing forceps on the forecoming head in 90 per cent of these. The general staff used forceps in 68 per cent of their primiparous vertex vaginal deliveries. The comparable figure for the house staff was 92 per cent. The obstetric staff used forceps in 64 per cent of their total vaginal deliveries, while the general staff had a 38 per cent incidence.

From the above figures, one will note an apparent relative reluctance on the part of the general staff to employ forceps. However, among forceps deliveries the general staff's midforceps incidence was 14.5 per cent, while that of the obstetrical staff was 5.8 per cent. If the relatively low over-all forceps incidence of the general staff is due to an attitude of conservatism, then it would appear inconsistent in that their midforceps incidence is higher.

We believe that saddle block analgesia had little effect on the increased incidence of midforceps among general staff deliveries, because, while the obstetrical staff handled 67.9 per cent of all private maternity cases, they employed 76.1 per cent of the saddle blocks used on these patients. The midforceps incidence for general staff deliveries under saddle block anesthesia was 18.7 per cent, while that for similar deliveries performed by the obstetrical staff was 8.8 per cent, which shows an approximately proportionate increased incidence in both groups.

Solid vs. Fenestrated Blades.—Solid-blade forceps were used by the house staff in 72.9 per cent of their forceps deliveries, by the general staff in 58.4 per cent, and by the obstetrical staff in 55.5 per cent. Table I shows the number of deliveries by each group of operators with solid-blade and fenestrated forceps and the percentages in each group of babies which were marked. It is at once clear that with the more popular solid-blade forceps, a lower percentage of babies was traumatized by each of the staff groups. Moreover, it will be noted (Table I) that solid-blade forceps in the hands of the least skilled group (i.e., the house staff) caused less superficial fetal trauma than did fenestrated forceps in the hands of the most skilled group (the obstetrical staff). It is likewise to be noted that a midforceps extraction with solid blades causes less superficial trauma than a low forceps extraction with open blades (Table II).

TABLE I. COMPARISON OF SOLID-BLADE WITH FENESTRATED FORCEPS (FIGURES INDICATE TOTAL NUMBER OF DELIVERIES AND PERCENTAGE OF BABIES MARKED IN THE RESPECTIVE GROUPS)

	SOLID BLADE	OPEN BLADE	TOTAL
House Staff	27 (51.8% marked)	10 (70% marked)	37 (56.8% marked)
General Staff	52 (32.7% marked)	37 (72.9% marked)	89 (49.4% marked)
Obstetrical Staff	183 (26.8% marked)	147 (59.9% marked)	330 (41.5% marked)
Total	262 (30.5% marked)	194 (57.7% marked)	

Table II is an analysis of low and midforceps deliveries with respect to the type of forceps. There were no cases of high forceps in our series. It will be noted from these and subsequent tables that solid-blade forceps caused consistently less superficial trauma than do fenestrated forceps in the hands of the same group, a fact which has long been well known but never before analyzed.

TABLE II. COMPARISON OF LOW AND MIDFORCEPS (FIGURES INDICATE NUMBER OF DELIVERIES AND PERCENTAGE OF MARKED BABIES IN EACH GROUP)

	SOLID BLADE		OPEN BLADE	
	LOW	MID	LOW	MID
House Staff	26 (53.9% marked)	1 (None marked)	10 (70% marked)	(Not used)
General Staff	44 (27.3% marked)	8 (62.5% marked)	32 (68.8% marked)	5 (100% marked)
Obstetrical Staff	171 (24.5% marked)	12 (58.3% marked)	140 (58.6% marked)	7 (85.7% marked)
Total	241 (28.2% marked)	21 (57.1% marked)	182 (60.9% marked)	12 (91.7% marked)

Table III is a breakdown of Table I into the specific types of forceps employed. It is apparent that the Tucker-McLean forceps are by far the most popular among all three groups. These and the Tucker-Luikart blades are the only solid-blade instruments employed at this hospital.

Table III also demonstrates that the general staff has a greater dependence on the small forceps (Hale, Hirst, and Sawyer) than do members of the obstetric staff. The general staff employed them in 23.6 per cent of their forceps deliveries, while the comparable incidence among the obstetric staff was 8.2 per cent. These forceps were, of course, designed merely to aid in extension of the fetal head by "lifting" the head over the perineum and in this sense are used simply as a preliminary to Ritgen's maneuver. The higher incidence of multiparas among the general staff may account in part for the increased incidence.

Malapplications.—In our series, the obstetric staff delivered 330 babies, 10 of whom were marked as a result of distinctly malapplied forceps, an incidence of 3.03 per cent. Of the 89 babies delivered by the general staff 13 were marked by malapplied forceps, a 14.6 per cent incidence. Since the location of marks on the babies' heads in many cases was our only index to malapplication, we have not attempted to compute the incidence of marked babies among total malapplications. It would not seem unreasonable to assume, however, that malapplications evoke a higher incidence of marks than do correct applications.

The validity of our assumption is shown by the findings, not included in the figures on total malapplications, on babies delivered in the posterior position. Of the 330 babies delivered by obstetrical department members, 3 were forceps extractions with the head inadvertently in the occiput posterior position, a rate of 0.9 per cent; 2 of the babies were marked. Of the 89 forceps deliveries by the general staff, 1 baby was extracted in the occiput transverse and 3 (one intentional, noted later) in the occiput posterior position, a total rate of 4.5 per cent; all of them were marked.

The total absence of forceps cuts, malapplications, and occiput posterior extractions among the patients delivered by the house staff may be in part attributed to the fact that their deliveries were closely supervised.

Rotations.—Fifteen forceps rotations were done with solid-blade forceps, and of these babies 73.3 per cent were marked. In the 13 rotations which were

TABLE III. COMPARISON OF DIFFERENT TYPES OF FORCEPS (FIGURES INDICATE THE NUMBER OF DELIVERIES WITH EACH TYPE OF FORCEPS AND THE PERCENTAGE OF MARKED BABIES IN EACH GROUP)

	SOLID BLADES		FENESTRATED BLADES							
			LARGE OPEN BLADE					SMALL OPEN BLADE		
	TUCKER-MC LEAN	TUCKER-LUIKART	SIMPSON	KIELLAND	ELLIOTT	DE LEE	GILLESPIE	HIRST	SAWYER	HALE
House Staff	22 (54.5% marked)	5 (40% marked)	1 (100% marked)	1 (100% marked)	2 (50% marked)	(Not used)	(Not used)	2 (50% marked)	4 (50% marked)	(Not used)
General Staff	49 (32.6% marked)	3 (33.3% marked)	2 (100% marked)	(Not used)	14 (78.6% marked)	(Not used)	(Not used)	9 (55.5% marked)	2 (100% marked)	10 (70% marked)
Obstetrical Staff	156 (26.3% marked)	27 (29.6% marked)	13 (46.2% marked)	4 (50% marked)	32 (71.9% marked)	47 (61.7% marked)	14 (42.8% marked)	16 (62.5% marked)	8 (37.5% marked)	13 (69.2% marked)
Total	227 (30% marked)	35 (31.7% marked)	16 (56.2% marked)	5 (60% marked)	48 (72.9% marked)	47 (61.7% marked)	14 (42.8% marked)	27 (59.3% marked)	14 (50% marked)	23 (69.5% marked)

done with fenestrated instruments (all by obstetric staff members), 76.9 of the babies were marked.

In the entire series of 456 forceps deliveries, there were no cases of failed forceps or of forceps slipping. One attempted rotation with Hale forceps failed, and the baby was extracted purposely as occiput posterior. The incidence of forceps rotation among the general staff's instrumental deliveries was 5.6 per cent; among the obstetric staff, 6.4 per cent.

Severity of Markings.—Among the 44 babies marked by the general staff, 7, or 15.9 per cent, sustained relatively severe marks. Such marks consisted of superficial abrasions and/or true cuts to or through the basal layer of the epidermis. Of the 137 babies marked by the obstetric staff, 7, or 5.1 per cent, sustained marks of such severity. Table IV analyzes these more severe marks in regard to the individual forceps and groups of operators.

The decreased number of severely traumatized babies, in contrast to the number twenty years ago, may be ascribed to two factors: (1) increased knowledge in the use of forceps and (2) the use of cesarean section in many cases which would previously have been difficult midforceps deliveries.

TABLE IV. (FIGURES INDICATE THE NUMBER OF MARKED BABIES WHO SUSTAINED RELATIVELY SEVERE MARKS FROM FORCEPS OPERATIONS AND THE PERCENTAGE THEY COMPRISE OF THE NUMBER OF MARKED BABIES IN EACH GROUP)

	SOLID BLADE	OPEN BLADE
General Staff	2 (11.76%)	5 (19.2%)
Obstetrical Staff	3 (6.12%)	4 (4.5%)
Total	5 (7.6%)	9 (7.9%)

Comment

Although our series is small, we believe that our figures are a fair index to the results obtained from the use of solid-blade forceps as compared with fenestrated forceps.

According to Dennen,[3] the fetal size and the degree of molding of the head should influence one's choice of the appropriate instrument in a forceps extraction. Not keeping this recommendation in mind, the occasional accoucheur at times reasons rather speciously that a little instrument would do little damage. Unfortunately, in our series the smaller forceps, Hale, Hirst, and Sawyer, are open bladed. As we have shown, the fenestrated forceps cause more superficial trauma and trauma of a severer degree than do the solid-blade forceps. Likewise, we have shown that fenestrated forceps in the hands of a skilled operator cause less fetal trauma than in the hands of the occasional accoucheur. It would not seem illogical to conclude, therefore, that the forceps which cause a higher incidence of superficial marking would in the long run be more likely to cause facial nerve paralysis or permanent forceps marks on the child's head. In our series, however, there was no demonstrable permanent damage of any kind to the infants, the one case of facial palsy having cleared by the time the baby was discharged. There were no cases of apparent intracranial damage from forceps procedures.

In addition to the above arguments in favor of wider use of the solid-blade obstetrical forceps, we wish to re-emphasize their well-known advantages of being easier to apply and easier to remove in the performance of Ritgen's maneuver.

Conclusions

As is generally known and as our survey shows, solid-blade forceps cause far less superficial fetal trauma than fenestrated forceps.

The less skilled obstetricians using solid blades mark fewer babies than the more skilled obstetricians using open blades.

Midforceps deliveries with solid blades are accompanied by a smaller percentage of marked babies than are low forceps deliveries with fenestrated forceps.

In our series the less skilled groups (house and general staffs) marked more babies with obstetric forceps than did the specialists, even though the former employed the less traumatic, solid-blade forceps in a higher percentage of their deliveries. The general staff also had a higher incidence of malapplications than did the obstetric staff.

In view of the above findings, we feel that, in general, forceps with solid blades or with the Luikart modification should be used: (1) when the diagnosis of the exact fetal head position is in doubt; (2) by the occasional obstetric operator; (3) in training interns and residents.

The possibility of such minor markings should not, however, deter one from using "prophylactic low forceps" to shorten the second stage of labor.

Although there were no cases of slipping of solid-blade forceps in our series, we do not mean to condemn the use of fenestrated forceps, which give a more stable purchase of the fetal head. We feel, however, that even in difficult cases, a solid-blade instrument should first be tried, especially by the less skilled operator. In breech deliveries, fetal facial trauma is one of the least considerations; in view of the admitted likelihood of slipping of the solid-blade instrument, a fenestrated blade should be used.

We wish to express our gratitude to Drs. Reuben A. Zarrilli, Loyola M. Donely, Robert H. Potts, Jr., and Stuart A. Weiss, members of the house staff of the Southern Baptist Hospital, whose cooperation made this study possible.

References

1. Adair, Fred L.: Quarterly Bulletin of the American Committee on Maternal Welfare 10: April, 1949.
2. Kamperman, George: Am. J. Obst. & Gynec. 60: 242, 1950.
3. Dennen, Edward H.: Bulletin of the Margaret Hague Maternity Hospital 3: June, 1950.

4414 Magnolia Street

THE CYTOLOGICAL SIGNIFICANCE OF HYPERESTRINISM*†

E. L. HECHT, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, the Post-Graduate Medical School, New York University-Bellevue Medical Center)

THIS paper proposes to describe a new diagnostic approach to certain gynecological disorders. It entails the picture of hyperestrinism as revealed by the vaginal smear, in its relation to fibromyomas, glandular cystic hyperplasia of the endometrium, and certain ovarian tumors. Throughout the paper, hyperestrinism will be considered in its cytological frame of reference, and should not be confused with absolute hyperestrinemia.

Cytological studies of the vaginal smear were first introduced in 1847 by Pouchet,[1] who attempted, with unstained smears, to analyze the normal human sex cycle. Since precise staining and preservation of the cellular elements are of paramount importance in accurate evaluation of the smear, the procedure was discarded. In 1916, Stockard and Papanicolaou[2] revived interest in such studies by developing a simple and effective method of fixation and preservation of cellular material on slides.

The utilization of the trichrome Masson stains enabled these investigators to make extensive studies of the vaginal smear in the laboratory animal, and in women during the normal estrous cycle as well as in various pathological conditions. These observations were published in an extensive and scholarly monograph by Papanicolaou[3] as a supplement to the *American Journal of Anatomy* in 1933.

In the past several years, the cytological method has been used preponderantly in the study of malignant cells. The potential of the vaginal smears has been tapped only superficially. A rich field of investigation in relation to gynecological endocrine dysfunction and to gynecological disorders other than malignancy remains to be explored.

Every gynecologist appreciates the difficulty encountered in making an early diagnosis of a fibroid uterus, glandular cystic hyperplasia of the endometrium, carcinoma of the endometrium, and various ovarian tumors. It is unlikely that suspicion will be aroused when no clinical signs or symptoms exist. Frequently, by the time a diagnosis is obvious, the patient has had some symptoms—no matter how slight—for a long time, and the disease has advanced to a point where the incidence of effective cure is reduced. We believe that the picture of hyperestrinism as seen in the vaginal smear not only tends to indicate the presence of these diseases, but, when persistently found, serves as a warning of impending pathology even in the absence of other positive findings.

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Material

From Jan. 1, 1948, through Jan. 1, 1950, 4,461 cytological interpretations were made at the Post-Graduate Medical School of New York University-Bellevue Medical Center (Fig. 1). Each of these 4,461 examinations represented a different case; each had at least 1 cervical and 1 vaginal smear, and, in many instances, 3, 4, or 5 slides. Occasionally, repeated sets of smears taken on different occasions were examined before a final diagnosis was established. The smears were all taken by standardized methods and all those unsatisfactory were repeated before an interpretation was attempted. The patients comprised hospital ward patients, hospital outpatient department patients, hospital private patients, and private patients of outside doctors. Some of the reasons for requesting cytological examination were: routine, sterility, malignancy, abnormal bleeding, menopause, infection, polyps, and pregnancy.

	SYMPTOMS		CLINICAL DIAGNOSIS		PROVEN HISTOLOGIC.			
PATHOLOGY	NO. OF CASES	PERCENT	NO. OF CASES	PERCENT	NO. OF CASES	PERCENT	AVERAGE AGE (IN YEARS)	AGE RANGE (IN YEARS)
FIBROID UTERI	116	48.73	238	66.86	150	63.02	41.6	27-61
GLANDULAR CYSTIC HYPERPLASIA OF ENDO.	40	67.79	59	16.57	34	57.62	36.4	23-58
CARCINOMA OF ENDO	7	77.77	9	2.53	9	100.	57.	37-64
CARCINOMA OF CX.	3	75.	4	1.12	4	100.	40.	34-48
CARCINOMA OF OVARY	2	100.	2	.56	2	100.	48.	42-55
OVARIAN CYST	3	50.	6	1.69	4	66.	38.	26-44
NO PATHOLOGY	0	0	38	10.67	0	0	35.	23-54

TOTAL NUMBER OF CASES 4461

INCIDENCE OF HYPERESTRINISM 356 (8%)

Fig. 1.—Analysis of findings in 356 cases of hyperestrinism, diagnosed by the vaginal smear.

The examiners comprised five practicing physicians, qualified to interpret smears by one to twelve years' training in cytology. In questionable cases, all five examiners consulted before a final diagnosis was made. The smears were prepared in the standard fashion and stained by the Papanicolaou method using Harris hematoxylin, OG 6, and EA 50.

Our diagnostic criteria for hyperestrinism are twofold: (1) at least 90 per cent of the cells present must be from the superficial layers, and at least 90 per cent of these must show a uniform eosinophilic staining cytoplasm; (2) the nuclei of these cells must be small and pyknotic.

It should be understood that two types of superficial cornified cells may be found in the picture of hyperestrinism. The morphological characteristics of one type are their polygonal forms, large size, and sharply defined edges; the cytoplasm appears delicate, homogeneous, transparent, and stains a bright red-orange. The other type comes from a deeper cell layer. Its morphological and staining characteristics are like those of the first type, with the exception of the cytoplasm which stained a deep red speckled with fine or coarse basophilic granules. These cells, the "granular cornified cells," come from the so-called cornified zone of Diercks, which is actually a zone of cellular condensation lying at and below the base of the superficial cornified layers of epithe-

lium. Such cells are observed only in small numbers and only when marked cornification is present, reflecting intense estrogenic activity.

At no phase in the normal menstrual cycle do we see complete uniform eosinophilia of the superficial cells with pyknosis of the nuclei. It is approached at the height of follicular activity, but, even at this time, generally 30 to 40 per cent of the superficial cells take a basophilic stain. In addition, this phase is very short-lived, so that examination of smears on successive days will usually show definite changes. In cases of hyperestrinism, however, the cells reveal an excessive degree of cornification which is constant.

Two conditions which give a false picture resembling hyperestrinism were carefully screened from these studies: (1) In the presence of any severe infection, it is not unusual for the cytoplasm of the superficial cells to show an excessive degree of eosinophilia. (2) When smears are dried before immersion in the fixative, the same picture is produced.

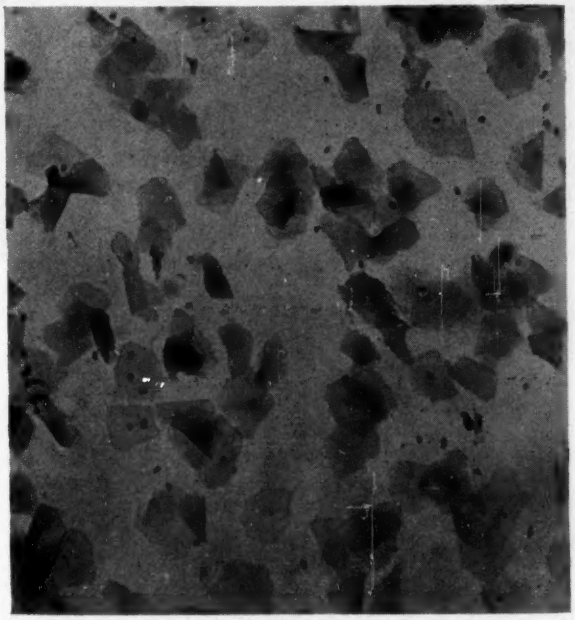

Fig. 2.—Hyperestrinism: all cells superficial in morphology, cytoplasm uniformly eosinophilic, and nuclei pyknotic. From a 41-year-old patient 26 days postmenstrual with myomas of the uterus.

Our observation revealed that 356, or 8 per cent, of the 4,461 cases presented a picture of hyperestrinism on both the cervical and vaginal smears. It soon became apparent that more than a coincidental number of these patients had definite gynecologic pathology.

1. Of the 356 cases of hyperestrinism, 238, or 66.86 per cent, were diagnosed clinically as myomas of the uterus, although only 116, or 48.73 per cent, presented symptoms referable to myomas—such as bleeding and pain (Fig. 2). The diagnosis in 150, or 63.02 per cent, of these was confirmed by operation and histologic examination. The average age of this group was 41.6 years, the youngest being 27 and the oldest 61. Sixteen, or 6.72 per cent, were postmenopausal; none of these was bleeding.

2. Of the 356 cases, 59, or 16.57 per cent, presented the cytological pattern of glandular cystic hyperplasia of the endometrium, 34, or 57.62 per cent, of which were so diagnosed by the pathologist (Fig. 3). The average age of

this group was 36.4 years, the youngest being 23 and the oldest 58. Forty patients, or 67.79 per cent, were bleeding abnormally. Four, or 6.76 per cent, of this group were postmenopausal, and all four had abnormal bleeding. Two of these gave a history of interrupted estrogenic therapy for one and three years, respectively.

It is extremely difficult to differentiate between glandular cystic hyperplasia of the endometrium and myomas of the uterus on cytological examination. Smears from patients with hyperplasia show clusters of benign endometrial cells in a field of excessively cornified superficial cells. The endometrial cells appear at any phase of the cycle and not as they normally do, at the time of menstruation only. Patients with submucous myomas or endometrial polyps may present exactly the same cytological picture. However, smears with persistent pictures of hyperestrinism without the presence of endometrial cells were more usually associated with the diagnosis of myomas of the uterus.

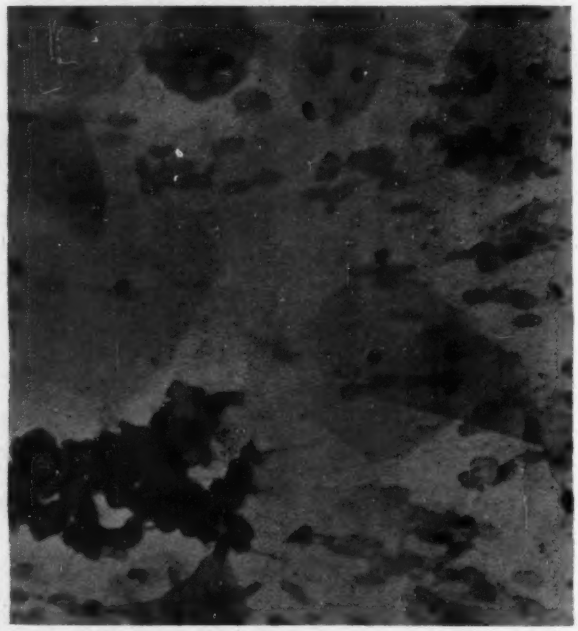

Fig. 3.—Glandular cystic hyperplasia of the endometrium in a 31-year-old patient. Smear taken on nineteenth day postmenstrual showing clusters of endometrial cells and red blood cells in a field of superficial cornified cells.

3. Of the 356 cases of hyperestrinism, 9, or 2.53 per cent, had carcinoma of the endometrium (Figs. 4 and 5). Eight were diagnosed cytologically as adenocarcinoma with hyperestrinism. The remaining malignancy was missed cytologically and subsequently diagnosed by curettage. The average age for the group was 57 years, the youngest being 37 and the oldest 64. Six, or 66 per cent, were postmenopausal. Seven of the 9, or 77 per cent, presented symptoms of abnormal bleeding. Three of these cases, or 33.3 per cent, also showed the histological pictures of glandular hyperplasia of the endometrium. Two, or 22.2 per cent, had fibroids.

Early carcinoma of the endometrium is extremely difficult to diagnose. A history of delayed menopause or dysfunctional flowing may be offered, while a history of treatment for uterine myomas may be suggestive. A patient with menorrhagia during the climacterium is 3½ times more likely to

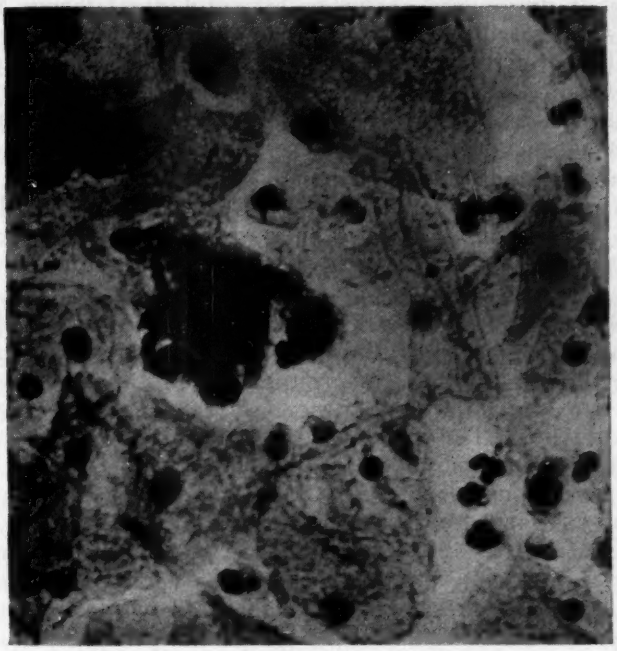

Fig. 4.—Carcinoma of endometrium in a 36-year-old patient taken the nineteenth day postmenstrual showing carcinoma cells in a field of superficial cornified cells.

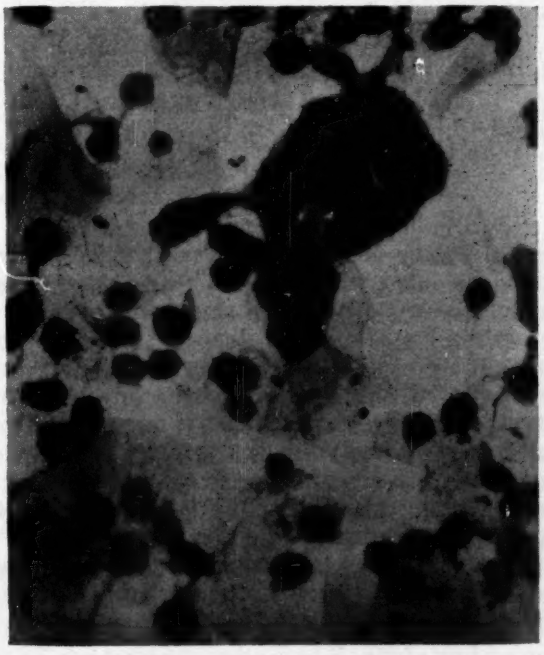

Fig. 5.—Carcinoma of the endometrium in a 64-year-old patient 14 years postmenopausal showing carcinoma cells in a field of superficial cornified cells.

have carcinoma of the endometrium than one who has no increased bleeding.[4] The percentage of diagnostic accuracy by cytological means is less for carcinoma of the endometrium than for carcinoma of the cervix. In carcinoma of the cervix, the percentage of accuracy ranges from 85 to 95 per cent, while in carcinoma of the endometrium it is 80 to 90 per cent. A negative smear does not exclude the possibility of carcinoma, and a positive finding does not always indicate operation, since an occasional false positive is inevitable.

All of these nine cases of carcinoma of the endometrium presented the cytological picture of hyperestrinism. It is not to be assumed that this will always be true in carcinoma of the endometrium. Hyperestrinism in postmenopausal patients, however, should initiate a thorough search for further pathology.

4. Of the 356 cases of hyperestrinism, 4, or 1.12 per cent, had carcinoma of the cervix, all of whom were diagnosed cytologically. The average age of these four patients was 40 years, the youngest being 34 and the oldest 48. All four had borne children. Three of these, or 75 per cent, had vaginal discharge and irregular spotting. The patient who presented no symptom was discovered only by the routine cytological examination. In two of these cases, the hyperestrinism was considered "not true," but rather as a result of the marked infection associated with the carcinoma.*

5. Of the 356 cases of hyperestrinism, in 6, or 1.69 per cent, there were clinical findings of ovarian cysts, 4, or 66 per cent, of which were proved histologically. Three of these were follicle cysts, while one was a dermoid. The average age for the group was 38 years, the youngest being 26 and the oldest 44. Three, or 50 per cent, gave histories of abnormal bleeding.

6. Of the 356 cases, 2, or 0.56 per cent, had carcinoma of the ovary. In one, an advanced carcinoma of the ovary with regional metastases, malignant cells as well as hyperestrinism were evident on the smear. These patients were 42 and 55 years of age, respectively, the average being 48 years. Both presented symptoms.

7. The remaining 38 instances in which hyperestrinism was diagnosed by the smear remained unexplained. The average for this group was 35 years, the youngest being 23 and the oldest 54. The smears in this group were taken routinely to rule out malignancy.

Comment

A cytohistological entity called hyperestrinism has been described. This picture, characterized by large masses of cornified superficial cells with small pyknotic nuclei is unlike any other in normal smears from normal women at any time of the menstrual cycle. *It is definitely a pathological pattern.*

An analysis of 4,461 consecutive cases revealed first that hyperestrinism is not rare, appearing in 356, or 8 per cent of the total. It showed further that 89.33 per cent of these had pathology—most commonly fibroids and glandular cystic hyperplasia of the endometrium. A smaller number, 4.78 per cent, was associated with ovarian cysts. In 10.67 per cent no pathology was found.

It is our belief that the presence of hyperestrinism in the vaginal smear is indicative of sustained, excessive estrogenic activity. Furthermore, since most patients whose vaginal smears revealed hyperestrinism also had pathology, we believe this cytopathological picture expresses an early stage of dysfunction characteristic of hemorrhagic uterine disease.

*This observation is contrary to Ayre's[5] finding, in which he showed a greater incidence of cornification of the superficial cells on cervical smears made from patients with carcinoma of the cervix. We feel that no such relationship exists. The cervix carcinoma cases are included in this study, however, simply because these patients also presented hyperestrinism. We do not feel that any relationship exists between hyperestrinism and carcinoma of the cervix.

There have been many attempts to relate by experimentation high estrogenic content in the blood with certain diseases. The original hormonal theory of the etiology of fibroids was based on an excessive secretion of estrogen.[6] This theory was first described years ago, and many reports have since been made. The theory has been supported by experiments with the guinea pig, in which administration of estrogens produced tumors not necessarily restricted to the genital tract.[7, 8] There is as yet no wholly conclusive evidence to support this association.

Some studies seem to indicate that the excessive administration of estrogen may be the precipitating factor in the production of adenocarcinoma of the endometrium. Speert[9] in 1948 found glandular cystic hyperplasia of the endometrium a common precursor of carcinoma, although the carcinoma occurred in only a small proportion of women with hyperplasia. Of 56 patients with endometrial carcinoma, 7 gave a history of estrogenic therapy for periods ranging up to five years. According to these studies, prolonged and unmodified estrogenic stimulation may thus seem to favor the development of endometrial carcinoma.

When the liver is diseased, as Biskind[10-13] has pointed out, it fails to metabolize and destroy estrogen. The large amount of circulating estrogen creates an overload which causes uterine bleeding. In 1949, Speert[14] reported cirrhosis of the liver in 4 out of 12 women with primary carcinoma of the endometrium, but in only one out of 54 with metastatic carcinoma of the uterine fundus. This is circumstantial evidence corroborating the view that abnormal and persistent estrogenic stimulation is a factor in the pathogenesis of endometrial carcinoma.

Thiessen[15] reviewed the findings in the endometria obtained by curettage and at operation for fibroids in the gynecological clinic at Freiburg from 1936 to 1947. Out of 186 cases, 71 per cent were associated with glandular cystic hyperplasia.

It is known that a definite relationship exists between certain feminizing tumors of the ovary and excessive amounts of estrogen in the blood. Granulosa-cell tumors in preadolescent children may cause precocious development of secondary sex characteristics, and these same tumors in older women may cause excessive bleeding; hyperplastic endometria have been found probably as the result of excessive estrogenic stimulation.

We feel that the vaginal mucous membrane is a highly sensitive reflector of estrogenic activity. In many ways it is more delicate and a more clear-cut and definite reporter than is estrogenic assay. Estrogenic assay is a complicated procedure, possible only in well-equipped laboratories, and not accessible to every doctor. In any case, bio-assays have doubtful diagnostic value. The normal range of estrogenic secretion is so great that estrogen assays have little significance for any particular patient. Jailer[16, 17] found that women in the menopause excrete about the same amount of estrogen as women with amenorrhea or normal women between peaks of excretion during the menstrual cycle. An assay by Knight[18] of a thecoma which might be expected to yield a large amount of estrogen contained only 0.2 gamma of estrone per 100 grams of tissue. The vaginal smear, we believe, is a far more reliable mirror of estrogen production, and it is easier to perform. The interpretation of the smear is based on definite, valid criteria, and its diagnostic value will increase as its use in routine examination becomes a part of gynecological practice.

Fifty per cent of the patients who had fibroids and hyperestrinism did not present any symptoms. What is the significance of this? When a persistent cytological picture of hyperestrinism is found, it may be hypothecated that these asymptomatic fibroids are functionally active and growing.

Our observations have also revealed that many patients with asymptomatic fibroid uteri do not present the cytological picture of hyperestrinism. Of what significance is this? We have not undertaken a study of fibroids, to determine how many did or did not present hyperestrinism, but we assume that these asymptomatic fibroids, without hyperestrinism, are not active, and are of no significance.

Conclusions

1. There is a cytological pattern seen in vaginal smears which is suggestive of hyperestrinism.
2. This picture is frequently associated with fibromyomas of the uterus, and with certain tumors and cysts of the ovary.
3. When seen with irregular showers of endometrial cells, it suggests glandular cystic hyperplasia of the endometrium.
4. In postmenopausal women, the finding of a hyperestrinism smear suggests further investigation for possible growing fibromyomas, or carcinoma of the uterus or ovaries.
5. These conclusions present a further argument for the use of the vaginal smear in gynecological practice.

References

1. Pouchet, F. A.: Théorie positive de l'ovulation spontanée et de la fécondation des mammiferes et de l'êspece humaine, basée sur l'observation de toute la série animale, Paris, 1847, J. B. Baillière.
2. Stockard, C. R., and Papanicolaou, G. N.: Am. J. Anat. **22**: 225, 1917.
3. Papanicolaou, G. N.: Am. J. Anat. **52**: 519, 1933.
4. Randall, C. L.: J. A. M. A. **127**: 20, 1945.
5. Ayre, J. E.: Am. J. Obst. & Gynec. **54**: 363, 1947.
6. Shute, E.: Canad. M. A. J. **51**: 443, 1944.
7. Nelson, W. O.: J. Endocrinol. **24**: 50, 1939.
8. Nelson, W. O.: Anat. Rec. **68**: 99, 1937.
9. Speert, H.: Cancer **1**: 584, 1948.
10. Biskind, M. S., Biskind, G. R., and Biskind, L. H.: Surg., Gynec. & Obst. **78**: 49, 1944.
11. Biskind, M. S.: Vitamins & Hormones **4**: 147, 1946.
12. Biskind, G. R., and Biskind, M. S.: Am. J. Clin. Path. **16**: 737, 1946.
13. Biskind, M. S.: Internat. J. Sex **2**: 30, 1948.
14. Speert, H.: Cancer **2**: 597, 1949.
15. Thiessen, P.: Geburtsh. u. Frauenh. **10**: 99, 1950.
16. Jailer, J. W.: J. Clin. Endocrinol. **8**: 564, 1948.
17. Jailer, J. W.: Endocrinology **43**: 78, 1948.
18. Knight, Wm. R.: Am. J. Obst. & Gynec. **56**: 311, 1948.

THE USE OF MUSCLE-RELAXING DRUGS IN COMPLICATED DELIVERIES*†

BRUCE R. AUSTIN, M.D., F.A.C.S., AND THOMAS W. MERING, M.D.,
WAYNESBURG, PA.

(From the Department of Obstetrics, Greene County Memorial Hospital)

THE purpose of this paper is to report the experiences of the authors in the use of two muscle-relaxing drugs, namely, Tubarine and Syncurine. The former is a highly purified form of curare, known as d-tubocurarine chloride. The latter is a synthetic muscle relaxant drug, decamethonium bromide, or as it is commonly known, C 10. It was hoped by the authors that in the use of these muscle-relaxing drugs at the time of complicated deliveries the amount of anesthetic necessary would be lessened; that much strain and trauma would be removed from the mother and baby; and that the mother's perineum at the time of her six weeks' checkup would be in much better condition than it would have been had the drugs not been used.

It is hardly necessary to go into the history of curare, for that has been completely covered by A. R. McIntyre in his recent book, *Curare; Its History, Nature, and Clinical Use.*[1] Syncurine is a new synthetic preparation which has very similar properties to curare, as it acts on the myoneural junction. It has been used extensively with general anesthesia in surgical patients. Its relaxing action is much faster and of shorter duration than any form of curare. It has been found to be free of histamine-like side effects, does not appear to have cumulative effects, and respiratory depression is generally much shorter in duration. Whether Syncurine passes the placental barrier or not has been debated.[2-4] It can be used along with almost any anesthetic agent. For practical purposes, 1 mg. Syncurine is equivalent to 3 mg. Tubarine. Syncurine, as far as it is known, has no definite antagonist. Neostigmine methylsulfate mitigates but does not completely abolish the effect of Tubarine.[5]

This paper will be divided into two parts, dealing with (1) the experiences with Tubarine and (2) the experiences with Syncurine.

Tubarine

In the delivery of fifty selected patients, Tubarine was used as an adjunct to the anesthetic. These patients were selected because of complications at the time of delivery such as long labors, malpositions, rigid soft tissues of the vaginal outlet, moderate contractions of the bony outlet, and conditions which made cesarean section advisable. All patients showing heart, lung, liver, or kidney disease were eliminated from the study.

Number of Cases.—Fifty.

Age.—Oldest, 35 years; youngest, 17 years; average, 22.7 years.

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†This study was supported by a grant from Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y.

Gravidity.—Primiparas, 38; gravida ii, 9; gravida iv, 3.

Anesthesia.—Nitrous oxide and oxygen, when used, were never over a 50:50 ratio.

Vaginal delivery: Gas-oxygen-ether, 30 cases; nitrous oxide and oxygen, 12; ether, 2.

Cesarean section: Six cases, in all of which gas-oxygen-ether anesthesia was used.

Medication Used During Labor.—

Vaginal delivery: Primipara: The average patient received during labor Demerol 300 mg. with scopolamine $\frac{1}{75}$ grain or Seconal 4½ grains with Demerol 150 mg. Occasionally rectal ether was used. Multigravida: The average patient received Demerol 200 mg., Seconal 4½ grains, and, occasionally, rectal ether.

Cesarean section: The average patient received Demerol 100 mg. and atropine sulfate $\frac{1}{150}$ grain approximately one-half hour before surgery, if the patient had not been in labor. In the latter part of the study, Demerol 50 mg. and atropine sulfate $\frac{1}{150}$ grain were found to be sufficient.

Administration of Tubarine.—Tubarine was given intravenously on an average of 12 minutes before vaginal delivery of the baby. The shortest time was 5 minutes, the longest time was 23 minutes. Relaxation was considered good in 83 per cent, fair in 14.5 per cent, and poor in 2.5 per cent. The fair and poor results were obtained in heavier patients in the early part of the study. Based on this experience, the following dosages were found satisfactory if administered during a two-minute interval: patients weighing 100 to 125 pounds should receive 4.5 to 6 mg.; 126 to 150 pounds, 6 to 7.5 mg.; 151 to 175 pounds, 7.5 to 9 mg.; 176 pounds or over, 9 mg. In cesarean section, 3 to 6 mg. of Tubarine were given intravenously when the patient was in a light plane of anesthesia.

Methods of Delivery.—Low forceps were used 19 times; outlet forceps, 12; low midforceps 6; midforceps 2; Scanzoni maneuver, 1; breech extraction, 2; spontaneous, 2; cesarean section, 6.

Reactions of Mothers.—In all vaginal deliveries Pitocin 0.5 c.c. was given after delivery of the baby and Ergonovine $\frac{1}{320}$ grain was given intravenously after delivery of the placenta. It was felt that the uterus was more responsive to these drugs when Tubarine was used because there was less general anesthetic given.

Respirations were usually slightly shallow just after Tubarine was given intravenously. This depended on the rate of administration of the drug.

Pulse rate showed no unusual change.

Relaxation of the perineum was usually evident 3 to 10 minutes after the drug was given and persisted for 15 to 20 minutes. The perineal muscles usually relaxed before the muscles of the lower extremities did and often the knee jerks were active when the perineum was relaxed.

Perineum: Right mediolateral episiotomies, 36; left mediolateral, 3; median, 3. In two cases the perineum was intact. There was no tendency for the episiotomy to extend or the vaginal mucosa to tear. The perineal muscles, being relaxed, did not retract, and the repair of the episiotomy could be carried out in an almost anatomical fashion. Blood loss at the time of episiotomy was minimal and seemed to be less than when Tubarine was not used. Two cases showed a paravaginal hematoma following forceps delivery. The relaxation of the perineum was fair in one case and poor in another. It was felt that a larger dose of Tubarine should have been used in both cases.

Nausea and vomiting when Tubarine was used were rare, both during and after delivery.

Uterine contractions were usually present.

Forced breathing with bag pressure was not needed and there were no intubations done.

In cesarean section, relaxation of the abdominal muscles was good in all cases.

Immediate Postpartum Course.—

Vaginal delivery: Of a total of 44 cases, 37 were uncomplicated, 2 showed an endometritis, 1 showed a phlebitis with endometritis, 1 had an indurated episiotomy, 3 had a morbidity which was unexplained. The longest hospital stay was 12 days, the shortest 5 days, the average 6.6 days. There were no muscular or nerve complications.

Cesarean section: Of a total of 6 cases, 4 were uncomplicated, 1 showed a bronchitis, and 1 showed a secondary anemia. The longest hospital stay was 12 days, the shortest 8 days, the average 10 days. It is believed that these results in vaginal and cesarean section deliveries were very good considering the type of cases that had been selected for study.

Six Weeks' Follow-up of Mothers.—Forty-three cases, or 86 per cent, were followed.

Vaginal delivery: Perinea were good in 37 cases, tight in 1 case, very tight in 1 case.

Cesarean section: Four were good. The other two cases were not followed.

Complications in all cases: One case, a vaginal delivery, showed subinvolution. Another case, a vaginal delivery with phlebitis, showed mild deep saphenous vein pain which cleared eleven weeks post partum. All in all, considering the types of cases selected, the vaginal outlets were in better condition and gave better support than would have been found had Tubarine not been used.

Newborn Infants.—

Immediate postnatal: The largest baby weighed 11 pounds, 6 ounces, and the smallest weighed 5 pounds. The average was 7 pounds, 8 ounces.

Vaginal delivery: Thirty-seven infants cried spontaneously; 4 needed respiratory stimulant, and 3 needed respiratory stimulant plus oxygen after delivery.

Cesarean section: Three infants cried spontaneously; 2 needed respiratory stimulant, and 1 needed respiratory stimulant plus oxygen. There were no signs of the effects of Tubarine in any of the infants. The infants who needed respiratory stimulants or oxygen were delivered from mothers who had had very heavy analgesia during their labor.

There were no deaths.

Six Weeks' Follow-up of Infants.—Eighty-four per cent of the babies were checked. The largest weighed 13 pounds, 4½ ounces; the smallest 7 pounds, 7 ounces; the average 10 pounds, 5 ounces. Two babies were pale; both were considered borderline premature cases at the time of delivery. Of the remainder, one baby showed a hydrocele and another showed thrush.

Syncurine

In this group sixty-seven cases were studied. No attempt was made to select cases but rather an attempt was made to study the mother and baby at the time of delivery and at their six weeks' follow-up. Patients with heart, lung, liver, or kidney disease were eliminated from the study.

Age.—Oldest, 36 years; youngest, 17 years; average, 24.3 years.

Gravidity.—Primiparas, 35; gravida ii, 20; gravida iii, 5; gravida iv, 34; gravida v, 1; gravida vi, 1; gravida vii, 1; gravida viii, 1.

Anesthesia.—The ratio of nitrous oxide and oxygen was usually 50:50.

Vaginal delivery: Gas-oxygen-ether, 24 cases; nitrous oxide and oxygen, 21 cases; ether, 1 case; rectal ether, 2 cases; no anesthesia, 1 case.

Cesarean section: Nitrous oxide, oxygen, and ether, 18 cases.

Medication Used During Labor.—This was similar to that used in the Tubarine study.

Administration of Syncurine.—

Vaginal delivery: Syncurine was given intravenously in doses varying from 1.5 to 3 mg. during a two-minute period. Average length of time before delivery was 8.5 minutes; shortest, 3 minutes; longest, 20 minutes.

Since Syncurine acts much more rapidly and lasts a shorter length of time than Tubarine, it was much more difficult to judge or gauge the dose of Syncurine to be given to a patient. In this group 76.5 per cent showed good relaxation; 21.2 per cent showed fair relaxation; 2.3 per cent showed poor relaxation.

Cesarean section: One or 1.5 mg. Syncurine was given intravenously after the patient was started with nitrous oxide-oxygen-ether anesthesia. If necessary, another milligram was given just before closure of the abdomen. Relaxation was good in all cases.

Method of Delivery.—Low forceps were used in 24 cases; outlet forceps, 12; low midforceps, 3; Scanzoni maneuver, 3; breech extraction, 3; spontaneous, 4; cesarean section, 18 cases.

Reactions of Mothers.—The oxytocics, Pitocin and Ergonovine, were used here as in the Tubarine study. The uterus responded well in each instance.

Respirations were usually slowed slightly, depending on rate of administration. Four patients had slight depression, 2 had moderate, 1 had severe depression. Artificial resuscitation with use of the bag pressure was necessary in the latter case. These changes in respiration were in cases delivered vaginally. No such change was found in cases delivered by cesarean section.

Uterine contractions remained strong in all cases wherein Syncurine was used. It apparently had no effect on the uterus or its nerve supply.

Blood pressure was recorded in 22 cases. There was lowering of approximately 10 mm. Hg in 5 cases and an increase of 10 to 20 mm. Hg in 10 cases. It remained unchanged in 7 cases. This variation in blood pressure usually was corrected in a very few minutes after delivery.

Pulse rate remained relatively unchanged in all patients except one who had no anesthesia and was relaxed with Syncurine. The pulse rate dropped from 90 to 60 but returned to normal as patient reacted and muscular movement returned.

Relaxation of the perineum: The method of measuring the relaxation of the vaginal outlet and perineal muscles was the same as in the Tubarine study, namely, by the decreased resistance to the examining hand. This was usually noticeable in from 3 to 8 minutes. When the perineal muscles were relaxed, so were the muscles of the lower extremities and the knee jerks were absent. It was difficult to determine the length of time that Syncurine was effective, but it was judged to be about 10 minutes.

All in all, it was felt that the relaxation of the perineal muscles was not as consistent as was noted with Tubarine. The action of Syncurine was variable and not dependable. In testing the perineal muscles and watching for relaxation, it was noted that many cases showed twitching of the anal sphincter.

Perineum: There were 38 mediolateral episiotomies and 2 median. In 9 cases episiotomy was not done; 7 of these had intact perinea and 2 cases showed a first degree laceration. There were 5 sulcus tears and 1 partial tear of the anal sphincter associated with episiotomies. In these cases, relaxation was fair to poor and the tear occurred on the side opposite the episiotomy.

There was also a tendency for extension of the episiotomy in many cases. In the use of Syncurine, the perineum did not seem to be as pliable or as relaxed as when Tubarine was used. Moreover, the repair of the episiotomy was not as easy when Syncurine was used as when Tubarine was employed.

Nausea and vomiting were rare both during and after delivery.

Uterine contractions continued practically as strong as if Syncurine had not been used.

Forced breathing with bag pressure was needed in one patient, who was purposely relaxed with only Syncurine and no anesthesia. She responded well to oxygen, delivered the baby spontaneously, and the baby cried spontaneously.

Cesarean section: In each of the 18 cases the abdominal muscles relaxed well. Uterine tone was excellent and closure of the incision was easy.

Immediate Postpartum Course.—

Vaginal delivery: Of a total of 49 cases, 44 were uncomplicated, 3 had endometritis, 1 had pyelitis, 1 had a mastitis. The longest hospital stay was 10 days, the shortest 3 days, and the average 6.1 days.

Cesarean section: Of a total of 18 cases, 14 were uncomplicated, 1 showed an endometritis, 1 showed a secondary anemia, 1 showed a pyelitis, 1 showed an unexplained morbidity. The longest hospital stay was 12 days, the shortest 7 days, the average 9.3 days.

Six Weeks' Follow-up of Mothers.—

Vaginal delivery: Thirty-eight cases were followed. Perinea were good in 31, satisfactory in 2, fair in 1, tight in 3. Two of these showed good perinea with rigidity and scarring, but functionally they were satisfactory. The other patient had to have a perineotomy later on. Two cases could not be evaluated because of multigravidity. In all cases healing was good, but in those cases with sulcus tears or extension of episiotomy there was a tendency toward inelasticity of the tissues.

Cesarean section: Five were followed and all were found to be in good condition.

Newborn Infants.—

Immediate postnatal: The largest baby weighed 10 pounds, 8 ounces; the smallest weighed 2 pounds, 12 ounces; and the average weighed 7 pounds, 4 ounces.

Vaginal delivery: Thirty-five infants cried spontaneously; fourteen were sleepy. In all cases in which stimulants or oxygen were needed, heavy analgesia had been used during labor.

Cesarean section: Fourteen infants cried spontaneously; 2 cried spontaneously and received some oxygen a short time after delivery; 2 received oxygen and lobeline after delivery. These four infants were delivered from mothers who had been in labor and had received analgesics before section. No positive sign of Syncurine effect was observed.

Chest study: In order to check pulmonary atelectasis, a study was undertaken wherein the chests of 50 babies were fluoroscoped within 24 hours after delivery. Twenty-five of these babies were delivered of mothers who had Syncurine at the time of delivery. There were no signs of atelectasis or of lung pathology which could be attributed to Syncurine. The 25 babies delivered from mothers who did not have Syncurine at the time of delivery showed normal heart and lung fields. No difference was noted between the two series.

Deaths: There were three deaths. One infant had a congenital absence of the right diaphragm and died on the eighth day. One infant (birth weight 2 pounds, 12 ounces) died of prematurity a few hours after delivery. The third, a spontaneous breech delivery, weighed 3 pounds, 4 ounces, cried vigorously at birth but died suddenly of prematurity 36 hours after delivery.

Six Weeks' Follow-up of Infants.—Forty-six babies were examined. The largest weighed 13 pounds, 7 ounces; the smallest 7 pounds, 1 ounce; the average 10 pounds, 8 ounces. Two were small and undernourished; 1 showed a right inguinal hernia and 1 showed facial eczema.

Summary

Tubarine.—

a. Tubarine, a highly purified form of curare, was used in fifty selected cases as an adjunct to anesthesia (nitrous oxide and oxygen, or nitrous oxide, oxygen, and ether) to provide muscle relaxation at the time of delivery. The results in vaginal delivery were: good, 83 per cent; fair, 14.5 per cent; poor, 2.5 per cent. The fair and poor results were obtained in heavier patients in the early part of the study. When larger doses were used as suggested in weight dosage table, the results were far better.

b. The average time interval of 12 minutes, lapsing between the intravenous administration of Tubarine and delivery of the baby, would indicate that the drug should be given after the physician has finished scrubbing, when he can watch the patient for signs of perineal relaxation.

c. Tubarine, from clinical observations, tends to relax the perineal muscles before the muscles of the lower extremities are affected.

d. There is much less trauma to maternal soft parts at the time of delivery, and repair of the episiotomy is much easier when Tubarine is used. The perinea, when checked six weeks post partum, were much better supported and healed than if Tubarine had not been used.

e. Positive signs of curarization in the newborn infant were not found; however, it is possible, since analgesics were used in most cases during labor, that early signs may have been masked by the analgesic agents. There were no deaths and the six weeks' examinations of babies were satisfactory.

f. No adverse reactions were noted. Uterine contractions were not inhibited and blood loss after delivery was probably decreased because of the ease with which the episiotomy was repaired.

g. The use of Tubarine in cesarean section cases gave good relaxation of the abdominal muscles, but the time lapsing between the beginning of the anesthesia, the injection of Tubarine intravenously, and the moment the baby could be delivered was felt to be too long.

Syncurine.—

a. Syncurine, a synthetic muscle-relaxing drug, was used in 67 cases: abdominal delivery, 18; vaginal delivery 49; as an adjunct to the anesthesia (nitrous oxide and oxygen, or nitrous oxide, oxygen, and ether) to provide muscle relaxation at the time of delivery. The results in vaginal delivery were: good, 76.5 per cent; fair, 21.2 per cent; poor, 2.3 per cent. Despite a variation in doses, the quick action of the drug, its short duration, and its seemingly variable effect on the perineal muscles made the standardization of dosage almost impossible.

b. The average time interval of 8½ minutes (longest 20 minutes and shortest 3 minutes) between the giving of the drug and the delivery of the infant indicates to some extent the variability with which the perineal muscles responded.

c. The anal sphincter muscles showed considerable twitching when Syncurine was used. The perineal muscles did not relax earlier than the muscles of the lower extremities.

d. No sign of Syncurine effect was observed in the newborn infant, but here again the analgesics used during labor may have masked any slight effect. Fluoroscopic chest studies on the infant, carried out within the first 24 hours

after delivery, showed no difference between babies delivered from mothers having Syncurine at the time of delivery and those delivered under the usual conditions. Six weeks' follow-up of babies showed good results.

e. No adverse side effects were noted when Syncurine was used. Uterine contractions continued strong. Blood pressure either stayed the same, dropped 10 mg., or increased 10 to 20 mg. Pulse rate remained about constant, respirations were occasionally moderately depressed.

f. The use of Syncurine in cesarean section proved almost ideal because of the good muscle relaxation obtained, light plane of anesthesia needed, and the quick action of the drug. No sign of Syncurine effect was observed in these babies.

Conclusions

1. The use of Tubarine (d-tubocurarine chloride) as an adjunct to the anesthesia, to relax the perineal muscles in difficult vaginal deliveries, is a safe procedure for mother and baby. It will reduce injury to the maternal soft parts and to the newborn infant. It allows a much lighter plane of anesthesia to be used.

2. The use of Syncurine (decamethonium bromide or C 10) at the time of cesarean section is a safe procedure for mother and baby. When used even in relatively small doses, it reduces the amount of anesthetic agent needed, gives good relaxation of abdominal muscles and, from clinical evidences so far available, has no effect upon the newborn.

3. In the use of muscle-relaxing drugs at the time of delivery, a skilled and experienced anesthetist is required. He must be equipped to do intratracheal intubation and artificial resuscitation by means of positive bag pressure, if the need arises.[6]

4. The authors would frown upon the indiscriminate use of muscle-relaxing drugs at the time of delivery.

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Addendum

Since the submission of this article, 25 cesarean sections have been done with Syncurine as an adjunct to anesthesia, with satisfactory relaxation of the abdominal muscles in all cases. The babies all breathed spontaneously.

References

1. McIntyre, A. R.: Curare: Its History, Nature, and Clinical Use, Chicago, 1947, University of Chicago Press.
2. Ellerker, A. R.: Brit. M. J. **2**: 398, 1950.
3. Katzman, Howard, and others: M. Ann. District of Columbia **18**: 561, 1949.
4. Hartnett, Leo J., and Freiheit, Harold J.: South. M. J. **43**: 277, 1950.
5. Unna, K. R., and others: J. A. M. A. **144**: 448, 1950.
6. Beckert, F. E., Fisher, C. W., and Harroun, P.: California Med. **68**: 19, 1948.

59 South Washington Street

ACUTE APPENDICITIS IN THE OBSTETRIC PATIENT*

H. D. Priddle, M.D., and H. Close Hesseltine, M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology, The University of Chicago and the Chicago Lying-in Hospital)

THE proper care of obstetric patients necessitates, in addition to adequate knowledge of this specialty, diagnostic abilities for the practice of general medicine and surgery. The surgical problems are many and varied. The majority of obstetric patients fall into the younger age group, and are thereby subject to surgical emergencies, one of which, acute appendicitis, many times requires skill to diagnose accurately and treat correctly.

Acute appendicitis in pregnancy is peculiar in the fact that physical findings may be almost nil, especially after the first trimester. The changes in the anatomical position and direction of the appendix during pregnancy were well studied by Baer, Reis, and Arens.[1] They noted as a rule a gradual rise of the appendix toward the right upper quadrant as pregnancy progressed. It is self-evident then that with a change of position of an organ, new relationships, symptoms, and findings may be expected. Even so, there are many exceptions to this usual course. The appendix may be retrocecal. It may be in the false pelvis, behind the uterus, or hang downward into the true pelvis. A left side position must not be forgotten. These phenomona mask the physical findings of acute appendicitis, particularly after the fourth month. The blood in pregnancy is abnormal in that there is normally a slight increase in the white blood cells and an increase in sedimentation rate. This blood picture must be recognized. The various reports of acute appendicitis give little import to a moderate leucocytosis, but place emphasis upon an increasing white cell count.

With uterine growth and displacement of the appendix, the differential diagnosis of pyelitis and appendicitis becomes more difficult. During pregnancy there is a physiological hydronephrosis, hydroureter, and urinary stasis, necessarily making the pregnant patient more susceptible to urological disease. The picture of appendicitis and acute pyelitis may be similar in the early stages before pyuria is present. The displacement of the appendix upward may give rise to tenderness and pain in the right flank and right upper quadrant.

Progression of gestation leads to a protrusion of the abdominal wall, generalized loss of tone in the rectus muscles, especially in the multipara. Spasm and rigidity of the abdominal wall are less likely to be found. Thus another physical finding has been lost to aid in diagnosis of acute appendicitis.

The nausea with or without vomiting in the early months of gestation may give rise to confusion in the history. The persistence of vomiting may bring about spasm of the rectus muscles. Nausea and vomiting of pregnancy or

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hyperemesis are absent after the fourteenth to sixteenth week of pregnancy. After the fifth lunar month, the onset of nausea and vomiting is definitely pathological and is not due to the pregnancy.

Material

The material for this study is composed only of those patients who had laparotomies because of diagnoses of appendicitis. All patients were seen in consultation by a senior member of the surgical staff of the University of Chicago Clinics. Since the opening of the Chicago Lying-in Hospital in 1931, there have been 41 cases in which patients underwent surgery with a clinical diagnosis of acute appendicitis in pregnancy or the early puerperium. There has not been one case of elective appendectomy during pregnancy for recurrent attacks of right lower quadrant pain. All of the patients reported herein were admitted because of acute attacks of abdominal pain which gave rise to tentative or positive diagnoses of acute appendicitis. In the series there are 19 patients under the age of 25 and all but 6 under 30 years of age. Of these 25, 20 were primigravidas. One patient who died had had five previous pregnancies.

The number of cases is small in comparison to that in other reports. An explanation may be that the fact that this is a maternity center and not a general hospital may lead patients who have not arranged for prenatal care to seek medical attention in the emergency room or at a local hospital because of an attack of abdominal pain. The majority of our cases are recent, especially since 1941. The explanation for which we can only conjecture, unless, since our number of deliveries has increased, we could statistically expect a greater incidence. In five different years, i.e., 1932, 1933, 1936, 1938, and 1939, there were no cases of acute appendicitis in pregnancy or the early puerperium.

Incidence.—The 41 cases in a period of nineteen years, during which time there were 59,403 mothers delivered from May, 1931, to March 31, 1950, represents an incidence of 0.069 per cent. Of these, only 26 carried a pathological diagnosis of acute appendicitis, a corrected incidence of 0.043 per cent. This is much lower than reports of Hoffman and Suzuki,[2] who had 0.106 per cent, or Mussey[3] at the Mayo Clinic with 2.0 per cent. Baer and associates report an incidence of 0.17 per cent in 16,543 pregnancies. In this series there was only one maternal death which will be summarized later.

Symptomatology.—The variability of symptoms can be noted in Table I. The typical history of acute appendicitis is missing in many instances, for nausea and vomiting is a frequent finding in the first trimester and many times this symptom is thought to be related only to the gestation. The pain location however, was typically right lower quadrant in 65 per cent of the cases, which is a lower percentage than in nonpregnant patients, nevertheless significantly high enough to be used diagnostically.

TABLE I. SYMPTOMS ON ADMISSION

SYMPTOM	NO. CASES	PERCENTAGE
Anorexia	5	10
Nausea	22	43
Nausea and vomiting	19	37
Location of pain.—		
R.L.Q.	33	65
Periumbilical	8	16
Fever	4	9
Chills	2	4
Diarrhea	5	10
Dysuria	6	12

Abdominal Findings.—The growth of the uterus may distort the abdominal findings by displacement of the appendix, and confusion may be caused by the changes in the abdominal wall. The experience of the surgical and the obstetric staffs agrees upon these findings which we feel are adequate in the differential diagnosis of acute abdominal pain. Table II illustrates the findings, one or more of which may have occurred in the same patient.

TABLE II

PHYSICAL FINDING	NO. CASES	PERCENTAGE
Muscle spasm	15	30
Right lower quadrant tenderness	33	65
Rebound tenderness	17	33
Bilateral lower quadrant tenderness	3	6
Right upper quadrant tenderness	1	2
No findings	1	2

The correct diagnosis of acute appendicitis was made in 28 instances, and the original but erroneous diagnosis was pyelitis in 4 cases, ectopic pregnancy in 2, twisted ovarian cyst in 3, gastroenteritis in 1, and, last, abdominal mass, etiology unknown, in 3. The primary diagnosis compares well with the pathological diagnosis in 26.

Laboratory Findings.—The normal physiological leucocytosis necessitates using only a rising leucocytosis as a diagnostic sign. The normal leucocyte count during pregnancy ranges between 8,700 and 12,500 white blood cells per cubic millimeter, and 27 per cent of our cases fell within this range. The highest count was 22,500 in what was found to be, after surgery, a case of pyelitis. The patient who died had as the highest white blood count before surgery 14,200, and only 15,800 the third day postoperatively. Postoperatively, 50 per cent of the patients had no white cell count above the usual range. Thus to us the laboratory findings during pregnancy are of less significance unless there is a definite rising leucocytosis within a few hours after the onset of symptoms.

Temperature.—The admission temperature was less than 38° C. in 32 cases and in only 2 cases was the initial temperature 39° or above. Postoperatively, the temperatures in 23 cases were less than 38° and likewise only 2 were 39° C., or above.

Treatment.—The policy of this institution is that, when there is doubt of the diagnosis of acute appendicitis, laparotomy is performed no matter what the duration of the gestation. The hospital admission of all patients in whom the diagnosis of acute appendicitis cannot be ruled out definitely will reduce greatly the risk of peritonitis due to delay. In perforation or abscess of the appendix the abdominal viscera do not wall off the inflammatory process properly because of the large vascular uterus which is freely movable and a periodically contracting structure. The uterus in turn appears to become irritated by the inflammation and proceeds to empty itself of the fetal contents. Observation of patients, without use of analgesics, in the hospital with frequent white blood counts, and with either a decrease or increase in abdominal pain, and/or changes in abdominal findings noted, for a short period of time, is imperative. If symptoms and/or signs progress, laparotomy is the procedure. By contrast it is a policy not to perform elective appendectomies during pregnancy for the care of so-called chronic appendicitis. It is known that the more severe the acute process, the lower incidence of previous attacks; conversely, the patient with chronic appendicitis has had previous attacks in the majority of cases. The routine appendectomy during pregnancy for chronic appendicitis is neither

good surgical nor good obstetrical procedure. Even though the risk is slight, nevertheless, a definite risk exists in any surgical procedure. By contrast, the danger of delayed surgery in acute appendicitis in the gravid or recently delivered patient has been well established. Experience has shown that removal of the appendix is far safer. There are minimal hazards of premature labor or abortion because of the surgery. True, normal appendices will be removed occasionally but the grave consequence from an appendiceal rupture warrants the occasional laparotomy at which time a relatively normal appendix is extracted. Appendectomy was performed in 39 cases, in one of which the appendix had ruptured probably during labor. Drainage of appendiceal abscess was done in the other 2. The incision generally used was McBurney's with or without Weir modification. Transverse incision was used in a very few cases in which the gestation was in the third trimester. The choice of incision must rest with the operator as each has its advantages. The preference for the McBurney incision is that if perchance labor should ensue before complete healing, herniation or evisceration is less likely to occur. Postoperative complications were few. Pyelitis occurred in four patients. One patient developed subsequently a subphrenic abscess which required a second hospitalization and drainage. There was one instance of wound infection, and one patient had a superficial thrombophlebitis.

As a postoperative routine, the patient is placed on bed rest with a liberal sedation for twenty-four to forty-eight hours, then gradually her activities are increased. Progesterone has not been employed postoperatively.

Antibiotics were used in only 13 cases and then prophylactically in all but 4. Crile[4] has reported on the successful treatment of peritonitis with penicillin, and Kennedy and associates[5] have had favorable results in 80 cases. It is possible that this therapy would be very beneficial in the gravid patient but as yet we have had no case for trial.

Duration of Pregnancy.—Acute appendicitis occurred in approximately equal numbers in each trimester of gestation as shown in Table III.

TABLE III

TRIMESTER	NO. CASES
First	15
Second	16
Third	15
Postpartum	5
Total	51

The policy of laparotomy when in doubt or of operation at any time during pregnancy has not brought about a great fetal loss. There were 2 instances in which premature labor ensued, one of which was in the early part of the last trimester and a viable premature infant was delivered who died the second day. In the second instance, labor began in the latter part of the second trimester with delivery of a previable premature. This to us changes the former thinking that laparotomy in the first trimester will lead to abortion, which did not occur in any of our cases. Formerly, many obstetricians and surgeons would procrastinate when a possible diagnosis of acute appendicitis was made in the first trimester, as abortion from exploration of the abdomen seemed a definite hazard. The 2 patients in whom premature labor did ensue, one thirty-six hours after surgery and the other the twenty-seventh day, had appendiceal abscesses, and thus had localized peritonitis at the time of surgery. Severe infections, and especially peritonitis, are known to predispose to premature labor or abortion. Thus one could have expected this course of events in both instances.

Fetal mortality of 2 in 36 undelivered patients, or 6.6 per cent, is much lower than is usually found in the literature, or if we use 26 cases of acute appendicitis with 2 fetal losses we still have only an 8.8 per cent loss. Hoffman[2] reported a fetal loss in acute cases of 17.4 per cent or three times our incidence. The remainder of our patients went to term with no fetal deaths.

Pathology.—The pathological diagnosis of acute appendicitis was made in 24 cases, which excludes the 2 appendiceal abscess cases, or 47 per cent. There were 25 instances in which the removed appendix was normal histologically. In one case a twisted but nonpalpable dermoid cyst explained the symptom; because of the obvious symptom the appendix was removed at the same time.

Maternal Mortality.—There was one maternal death in our series which occurred in 1931. Briefly the history of the case is as follows:

M. C. (Unit No. 45791), a 32-year-old gravida vi, para v, was first seen Sept. 8, 1931, in the outpatient clinic, with a history of abdominal pain, tenderness, and nausea and vomiting for four days. She had been amenorrheic since April 26, 1931. The patient was admitted to the hospital immediately.

Past history revealed that she had had two episodes similar to this eight years previously.

The physical examination on admission revealed temperature of 99° F., pulse 120, respiration 20, and blood pressure 110/62 . There were tenderness, voluntary rigidity in the right upper quadrant, and an indefinite mass palpable in this same area. There was no tenderness over McBurney's point. The uterus was at the level of the umbilicus. The various diagnoses made on admission were twisted ovarian cyst, retroperitoneal abscess, and hydrops of the gall bladder. Laboratory findings were a white blood count of 14,200 with 86 polymorphonuclear leucocytes and 24 lymphocytes. The urine was negative.

The patient was hydrated with normal saline and intravenous glucose and two days later under general anesthesia a laparotomy was performed and an abscess cavity was accidentally opened behind the ascending colon which contained 60 c.c. of purulent material. Two drains were inserted through the flanks.

Postoperatively the patient was given intravenous fluids, and Wangensteen suction for forty-eight hours. She recovered slowly and was discharged on the twenty-fifth postoperative day with abdominal wounds well healed.

Two days after discharge, she was admitted in active labor and after ten hours of labor delivered a 980-gram female infant that expired almost immediately. The placenta was sent to the pathology laboratory and a microscopic diagnosis of acute placentitis was made. Immediately after delivery the patient had a chill, temperature of 100.4° F., pulse of 120, and complained of right lower quadrant pain.

Three days later, because of increased pain and tenderness in the right lower quadrant, a drain was inserted through the old wound and a great deal of purulent material evacuated. This was on Oct. 10, 1931, and cultures from the material were reported as Streptococcus. Chest film taken this day was normal.

On Oct. 25, 1931, pelvic examination revealed a right pelvic mass extending upward under the cecal area. The pulse rate was 120. Four hundred c.c. of whole blood were given. Five days later, the pain and rigidity over the right side extended down into the femoral vessels. Five hundred c.c. of whole blood were given intravenously. Again a pelvic examination was done on Nov. 9, 1931, and the mass was felt in the right side, described as being fluctuant and now about the level of the iliac crest. Temperature was 104° F., pulse 150, respirations 28. Five hundred c.c. of citrated whole blood were given. She was being maintained on intravenous fluids.

The forty-first day after the second admission under local anesthesia a laparotomy was performed and a retroperitoneal abscess opened and two drains inserted. The patient's condition became progressively worse and on Nov. 14, 1931, she died. Autopsy was denied.

Summary

1. A review of 51 cases in which a clinical diagnosis of acute appendicitis was made during pregnancy or the early puerperium with one maternal death and two fetal deaths is reported. The signs, symptoms, and physical findings were discussed.

2. The obstetrician must always be alert to the signs and symptoms of acute appendicitis in pregnancy and when in doubt it is best to operate no matter what the duration of the pregnancy.

3. Laparotrachelotomy at the time of removal of an appendix, with but very few exceptions, is violation of good surgical procedure, and should not be performed.

4. It is an acknowledged principle that elective appendectomy at the time of cesarean section or removal of an ectopic pregnancy increases the hazard of appendectomy.

The authors express their appreciation to the members and residents of the Surgery Department for their consultations, diagnoses, and surgery over the many years. Special appreciation is offered to the following staff members: Drs. William Adams, H. P. Jenkins, Dwight E. Clark, and J. Garratt Allen.

References

1. Baer, Joseph L., Reis, Ralph A., and Arens, Robert A.: J. A. M. A. **98**: 1359, 1932.
2. Hoffman, Edwin S., and Suzuki, Masamichi: Grace Hosp. Bull. **26**: 25, 1948.
3. Twyman, R. A., Mussey, R. D., and Stalker, L. K.: Proc. Staff Meet., Mayo Clin. **15**: 484, 1940.
4. Crile, George, Jr.: Am. J. Surg. **72**: 859, 1946.
5. Kennedy, C. S., McCadie, J. H., and Arminski, T. C.: Grace Hosp. Bull. **25**: 107, 1947.

THE LEVELS OF SEVERAL METABOLITES IN BLOOD AND URINE DURING NORMAL PREGNANCY*

J. R. Beaton, M.A., M. J. Cavan, B.Sc., R. E. Lau, M.D., W. J. McGanity, M.D., E. W. McHenry, Ph.D., and G. L. Watt, M.D., Toronto, Ont.

(From the Departments of Public Health Nutrition and of Obstetrics and Gynecology of the University of Toronto)

OBJECTIVE laboratory evidence regarding the effects of pyridoxine in cases of hyperemesis gravidarum has been presented in a previous paper.[1] The data indicated some impairment in the utilization of at least one amino acid. As part of an extended study of abnormalities of protein metabolism during pregnancy, it was necessary to obtain evidence regarding the levels of several metabolites in the blood and urine of pregnant patients seemingly normal. The metabolites selected for study were: total amino nitrogen and urea in whole blood, glutamic acid in plasma, and 4-pyridoxic acid in urine. Amino nitrogen and urea were selected to obtain information regarding protein metabolism, glutamic acid because it might be an index of transamination, and 4-pyridoxic acid since it is the principal metabolite of vitamin B_6. An examination of the literature shows that there is a great deal of concordant information regarding the levels of blood urea in normal pregnancy, that there are conflicting data regarding blood amino nitrogen, and that there is a dearth of information regarding plasma glutamic acid and urinary 4-pyridoxic acid. For interpretation of data derived from cases of normal pregnancy it has been essential to secure corresponding information for normal men and for nonpregnant normal women.

Methods

Subjects.—Male subjects were mainly members of the staff of the School of Hygiene. Subjects classified as nonpregnant women were from the staff of the same institution and from the class of student dietitians of the Toronto General Hospital. Pregnant patients, apparently normal, were obtained from the Outpatient Clinic of the Toronto General Hospital; they were in various stages of pregnancy.

Blood and Urine Specimens.—Venous blood specimens were obtained generally with the subject in a fasting state. Coagulation was prevented by the use of heparin. Urine specimens were mostly first morning ones and were preserved with benzoic acid.

Analytic Procedures.—The methods used were as follows: amino nitrogen, a modification of the procedure of Folin[2]; urea, Archibald[3]; glutamic acid, Prescott and Waelsch[4]; 4-pyridoxic acid, Huff and Perlzweig.[5] Values reported below for 4-pyridoxic acid are expressed as the lactone.

*This study is part of a joint investigation on nutrition problems in pregnancy. The study has been made possible by a grant from the Robert Gould Research Foundation and by a Public Health Research Grant from the Department of National Health and Welfare of the Government of Canada.

Results

1. Blood Amino Nitrogen.—The amount of amino nitrogen in the blood has been used as an index of the quantity of nondeaminated amino acids. Experimental data are given in Table I. No sex difference in the level of blood amino nitrogen was found, but pregnancy had a significant effect, particularly in the first and second trimesters.

TABLE I. BLOOD AMINO NITROGEN IN MALES AND NONPREGNANT AND PREGNANT WOMEN

GROUP	NUMBER OF SUBJECTS	RANGE OF AMINO NITROGEN (MG. %)	MEAN AND STANDARD DEVIATION (MG. %)	SIGNIFICANCE OF DIFFERENCE, "t"
(1) Males	20	6.1-8.5	7.1 ± 0.64	
(2) Normal females	50	6.0-8.3	7.1 ± 0.61	
(3) Pregnant, first trimester	11	5.1-6.9	5.9 ± 0.58	(2) vs. (3) 6.0
(4) Pregnant, second trimester	26	5.3-6.9	6.0 ± 0.61	
(5) Pregnant, third trimester	20	5.4-9.3	6.5 ± 0.83	(3) vs. (5) 2.1

2. Blood Urea.—The level of blood urea is the result of the opposing effects of urea formation and of urea excretion. Previous work reported by us has been concerned with the sustained high level consequent to alanine administration in vitamin B_6-deficient animals[6] and in cases of hyperemesis gravidarum.[1] Data secured in the present study are given in Table II. No sex difference was observed. The low value of the mean for pregnant subjects is a confirmation of previous work[7] and is probably a reflection of the decrease in protein catabolism during normal pregnancy.

TABLE II. BLOOD UREA VALUES IN MALES AND NONPREGNANT AND PREGNANT WOMEN

GROUP	NUMBER OF SUBJECTS	RANGE (MG. %)	MEAN AND STANDARD DEVIATION (MG. %)
Males	22	14.8-31.0	22.6 ± 4.8
Females, nonpregnant	50	11.0-32.6	22.4 ± 9.0
Pregnant	90	6.6-29.8	15.9 ± 5.1

3. Plasma Glutamic Acid.—The data are given in Table III. It should be noted that the difference between the means for men and women is significant at the 5 per cent level and nearly so at the 1 per cent level. There is an apparent sex difference, but pregnancy seems to be without effect.

TABLE III. PLASMA GLUTAMIC ACID LEVELS IN MALES AND NONPREGNANT AND PREGNANT WOMEN

GROUP	NUMBER OF SUBJECTS	RANGE OF PLASMA GLUTAMIC ACID (MG. %)	MEAN AND STANDARD DEVIATION (MG. %)	SIGNIFICANCE OF DIFFERENCE, "t"
(1) Males	26	0.7-2.0	1.2 ± 0.33	
(2) Females, nonpregnant	51	0.5-1.8	1.0 ± 0.37	(1) vs. (2) 2.50
(3) Pregnant	67	0.4-1.9	1.0 ± 0.33	

4. Urinary Concentration of 4-Pyridoxic Acid.—Since 4-pyridoxic acid is an inactive metabolite of vitamin B_6, it has been assumed[8] that the total ex-

cretion of 4-pyridoxic acid is an index of the quantity of vitamin B_6 utilized in the body. A comparison of the total twenty-four-hour excretion of the metabolite with its concentration in samples of urine obtained from normal subjects at different times during the day has indicated that a measurement of metabolite concentration is as useful as is total excretion. The data given in Table IV are expressed in terms of concentration. Group I of pregnant cases consisted of patients in all trimesters; the subjects in Group II were selected as being shortly before parturition. It should be noted that there is a great variation in individual values with considerable overlapping in ranges for the various groups. However, the mean values for the two pregnant groups are similar and are significantly less than the mean for nonpregnant women. Observations in this laboratory indicate that the excretion of 4-pyridoxic acid does not return to the nonpregnant level until several weeks have elapsed after parturition.

TABLE IV. URINARY CONCENTRATION OF 4-PYRIDOXIC ACID LACTONE

GROUP	NUMBER OF SUBJECTS	RANGE OF 4-PYRIDOXIC ACID (γ/ML.)	MEAN AND STANDARD DEVIATION (γ/ML.)	SIGNIFICANCE OF DIFFERENCE, "t"
(1) Males	25	0.91-11.69	4.19 ± 2.87	
(2) Females, nonpregnant	50	1.31-16.62	6.15 ± 3.20	(1) vs. (2) 1.26
(3) Group I pregnant	65	0.86-19.09	3.39 ± 2.61	(2) vs. (3) 2.43
(4) Group II pregnant	35	1.09-10.67	3.21 ± 2.01	

Comment

It is generally assumed that pregnancy causes a decrease in protein catabolism and an increase in anabolism with considerable retention of protein in the body of the mother.[7] The low values for blood amino nitrogen and for blood urea are consonant with the assumed alteration in protein metabolism. The present study indicates that there is no alteration in the plasma level of glutamic acid and that the amount of 4-pyridoxic acid in the urine is significantly reduced. If 4-pyridoxic acid is the principal end product of the metabolism of vitamin B_6, it would appear that the utilization of this vitamin is decreased in pregnancy. Approximate estimates of vitamin B_6 intakes, calculated from total food intakes, have shown that the intakes of pregnant subjects were about the same as those of the nonpregnant women. It is interesting that a reduction in the utilization of vitamin B_6 occurred during a period of decreased protein catabolism. An inference could be drawn that vitamin B_6 is needed in smaller amounts during pregnancy; requirements of other nutrients are claimed to be increased during pregnancy.

Summary

A comparison of blood urea and amino nitrogen levels, of plasma glutamic acid levels, and of the concentration of 4-pyridoxic acid in the urine of men, nonpregnant women, and pregnant subjects shows that mean values for blood urea and for blood amino nitrogen are decreased in pregnancy, that pregnancy does not alter the mean level of plasma glutamic acid, and that the concentration of 4-pyridoxic acid in the urine is decreased significantly in pregnancy.

References

1. McGanity, W. J., McHenry, E. W., Van Wyck, H. B., and Watt, G. L.: J. Biol. Chem. **178**: 511, 1949.
2. Frame, E. G., Russell, J. A., and Wilhelmi, A. E.: J. Biol. Chem. **149**: 255, 1943.
3. Archibald, R. M.: J. Biol. Chem. **157**: 507, 1945.
4. Prescott, B. A., and Waelsch, H.: J. Biol. Chem. **167**: 855, 1947.
5. Huff, J. W., and Perlzweig, W. A.: J. Biol. Chem. **155**: 345, 1944.
6. Beaton, J. R., Ballantyne, R. M., Lau, R. E., Steckley, A., and McHenry, E. W.: J. Biol. Chem. **186**: 93, 1950.
7. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Interpretations, vol. I, Baltimore, 1946, Williams & Wilkins Company, p. 666.
8. Rabinowitz, J. C., and Snell, E. E.: Proc. Soc. Exper. Biol. & Med. **70**: 235, 1949.

CARCINOMA OF THE CERVIX IN JEWISH WOMEN

ALBERT ROTHMAN, M.D., LEONARD P. RAPOPORT, M.D., AND ISRAEL DAVIDSOHN, M.D., CHICAGO, ILL.

(From the Departments of Obstetrics and Gynecology and Pathology of the Chicago Medical School, and the Mount Sinai Hospital)

STATISTICALLY it has been recorded on numerous occasions that there is a significantly low incidence of carcinoma of the cervix in Jewish women. The reasons for this have been postulated by many, but proved by none. In 1939 one of us reviewed the more important world literature[10] on this subject and published the statistics of the Mount Sinai Hospital in regard to this subject. The present paper is a ten-year follow-up of our statistics.

Handley,[1] in 1936, attempted to incriminate phimosis or careless subpreputial hygiene as a possible cause of cervical carcinoma. He based his conclusions on findings in the Fiji Islands, where there were 90,000 natives, who are circumcised at puberty, and 70,000 immigrated Indians, who do not practice circumcision. These two groups do not mix or intermarry. In the hospital reports of Suva, Fiji, from 1925 to 1932, there were only three cases of cervical carcinoma in Fijian women and twenty-six cases in Indian women, an incidence eight times as great. He therefore concluded from this, and various statistics showing a lower incidence in Jewish women, that circumcision could lower the incidence of cervical carcinoma. Marsden,[2] while not presenting statistical analyses, does state that, in Malaya, carcinoma of the cervix is common in women of all races, including Moslems (who practice circumcision), except in Jewish women, in whom it is rare. Kennaway,[3] in his excellent review of the world literature, quotes Khanolkar from Tata Memorial Hospital (Bombay) as follows:

RACIAL GROUP	INCIDENCE OF CARCINOMA OF CERVIX
Hindus	44.0%
Moslems	20.7%
Parsees	14.8%
Indian Christians	12.7%

From this we see that the Moslems, who practice circumcision, have the second highest incidence, while the Christian group, who may or may not practice circumcision, have the lowest incidence. Thus, despite the fact that Plaut and his group[4] have shown the carcinogenic effect of horse smegma, the etiological role of circumcision is still debatable.

Wolff[5] compared the percentage of carcinoma in female genital organs and breasts between the general population of Berlin in 1932-1933 and the Jewish population in 1924-1926 and 1932-1934. He concluded: "It would appear that, proportionately, the women of Berlin have twice as much carcinoma of the uterus as Jewesses." However, his findings lose much of their value since he could not subdivide his results into carcinoma of the cervix and corpus.

Smith,[6] reporting from Memorial Hospital, New York, on 3,106 patients with primary cervical carcinoma, from 1916 to 1937, found an incidence of only 4.2 per cent in Jewish women, this group comprising 14.4 per cent of the

entire clinic (Table I). This is a significantly lowered incidence, when compared, for example, with the United States group, which has an incidence of 24.5 per cent while comprising 19.3 per cent of the clinic.

TABLE I. A COMPARISON OF NATIONALITY INCIDENCE IN PATIENTS WITH CERVICAL LESIONS AND WITH A CROSS SECTION OF THE ENTIRE CLINIC. SMITH[6]

	CERVIX		CLINIC	
	NO.	%	NO.	%
Negro	225	7.02	426	6.9
German	341	10.9	582	9.4
Italian	528	16.9	777	12.5
Jewish	132	4.2	1085	17.5
Greek	10	0.3	43	0.06
Irish	419	13.4	890	14.4
Polish	32	1.0	104	1.6
Scotch and English	330	10.6	439	7.1
Austrian	104	3.3	219	3.5
United States	764	24.5	1191	19.3
Others	221	7.1	412	6.6
Total	3,106		6,168	

Treusch, and associates,[7] at the Mayo Clinic, saw 568 consecutive cases of carcinoma of the cervix from 1938 to 1942. Of this group, 566 were not Jewish, while the remaining two were of unknown derivation. This assumes greater significance when we realize that the estimated Jewish registration at the clinic for that period was 7-8 per cent of the total.

Kaplan[8, 9] states that among 1,342 patients with carcinoma of the cervix seen in the Radiation Therapy Department (Bellevue Hospital) over a period of 21 years, only 25 (or 1.8 per cent) were Jewish.

Material

At Mount Sinai Hospital during the ten-year period of 1940-1949, female admissions, excluding newborn infants, numbered 49,407 (Table II). This group included 36,759 Jewish and 12,648 non-Jewish patients. In the latter group, 22 cases of carcinoma of the cervix were found, while in the larger group of Jewish patients, only 7 cases of cervical malignancy were uncovered.

TABLE II. DISTRIBUTION OF UTERINE CARCINOMA, OVER A 10-YEAR PERIOD (1940-1949), AT MOUNT SINAI HOSPITAL, CHICAGO

	JEWISH	NON-JEWISH	TOTAL
Female admissions (except newborn)	36,759	12,648	49,407
Percentage of total female admissions	74.4	25.6	100.0
No. of cases of carcinoma of cervix	7 (24.1%)	22 (75.9%)	29
Incidence of carcinoma of cervix within own group	0.019% (19:100,000)	0.174% (174:100,000)	0.059% (59:100,000)
No. of cases of carcinoma of corpus uteri	32 (82.05%)	7 (17.95%)	39
Incidence of carcinoma of corpus uteri within own group	0.087% (87:100,000)	0.055% (55:100,000)	0.079% (79:100,000)

Our statistics indicate that carcinoma of the cervix was nine times more frequent in the non-Jewish group as compared with the Jewish group of women, which is a statistically significant difference.

In this same group there were 32 instances of carcinoma of the endometrium in the Jewish group, and only seven cases in the non-Jewish group. Thus the incidence of endometrial carcinoma was statistically not significantly different in the two groups.

By comparison of our findings with those obtained by the National Cancer Institute[11] in a survey of the general female population of Chicago in 1947, it can be seen that our incidence is uniformly greater, as would be expected in a hospital population (Table III).

TABLE III. INCIDENCE OF CANCER OF THE CERVIX AND CORPUS UTERI IN THE GENERAL FEMALE POPULATION OF CHICAGO (1947)[11]

All uterus	55.8:100,000
Cervix uteri	31.6:100,000
Corpus uteri	8.1:100,000
Other and unspecified uterus	16.1:100,000

Of interest is the relatively large proportion (29 per cent) of unspecified lesions of the uterus. It appears likely, according to H. F. Dorn, that a major portion of these cases properly should be allocated to cervix.

Our findings corroborate the previous findings of one of us (I. D.)[10] and those of other investigators that carcinoma of the cervix is much less frequent in Jewish than in non-Jewish women. Our statistics are not absolutely accurate since we could not trace the ancestry of our patients.

These figures should not mislead one in managing lesions of the cervix in Jewish patients. There are those who are inclined to do supracervical hysterectomies simply because the patient is Jewish. Others neglect to do biopsies. Any patient with a cervix may develop a carcinoma. Statistical reports should be no factor in diagnosis and therapy.

Conclusions

1. Statistics at Mount Sinai Hospital, Chicago, over the period 1940-1949 revealed that carcinoma of the cervix is nine times as prevalent in non-Jewish as in Jewish women.

2. The incidence of carcinoma of the endometrium is not significantly different in Jewish women as compared with the non-Jewish group.

References

1. Handley, W. C.: Lancet 1: 987, 1936.
2. Marsden, A. T. H.: M. J. Malaya 2: 261, 1948.
3. Kennaway, E. L.: Br. J. Cancer 177, 1948.
4. Plaut, A., and Kohn-Speyer, A. C.: Science 105: 391, 1947.
5. Wolff, G.: Am. J. Hyg. 29: 121, 1939.
6. Smith, F. R.: AM. J. OBST. & GYNEC. 41: 424, 1941.
7. Treusch, J. V., Hunt, A. B., and Rousuck, A. A.: AM. J. OBST. & GYNEC. 52: 162, 1946.
8. Kaplan, I. I., and Rosh, R.: Am. J. Roentgenol. 57: 659, 1947.
9. Kaplan, I. I.: J. A. M. A. 141: 574, 1949.
10. Davidsohn, I.: Medical Leaves: 19, 1939.
11. Dorn, H. F.: Personal communication of data in process of publication.

710 SOUTH WOLCOTT AVENUE

THE TRANSVERSE DIAMETER OF THE INLET

D. Frank Kaltreider, M.D., Baltimore, Md.

(From the Department of Obstetrics, the University of Maryland, School of Medicine)

WHEN disproportion is present in an obstetrical patient, the inlet is most frequently the cause. In the prediction of inlet obstruction, the obstetrical conjugate is usually the factor considered. This is probably a holdover from the days when rickets played the major role in inlet difficulties. The transverse diameter has not been emphasized, or rather it has been neglected, as to its role in inlet contraction. It has been stated that the transverse diameter only occasionally causes dystocia at the inlet.[1] There are two methods that have been used to evaluate the transverse diameter along with the obstetrical conjugate, namely, the use of areas, as recommended by Mengert,[2] Allen,[3] and Nicholson,[4] and the use of the sum of the obstetrical conjugate and the transverse, as used by Weinberg and Scadron.[5] From clinical observation the transverse diameter seemed to be frequently at fault. For this reason it was thought desirable to determine its role, if any, in inlet obstruction.

Material and Methods

In this study there were 1,167 consecutive x-ray pelvimetries done on suspect pelves at the University Hospital, Baltimore, with the Steele and Javert isometric technique, between July 1, 1947, and June 30, 1950. These roentgenograms were analyzed from the viewpoint of difficulty with respect to the obstetrical conjugate, the transverse diameter, and a combination of the former and the transverse diameter in such a fashion as to place equal emphasis on these diameters. The obstetrical conjugate is defined as the shortest distance between the posterior surface of the upper portion of the symphysis pubis and the anterior surface of the upper portion of the sacrum. The transverse diameter is measured at right angles to the obstetrical conjugate at the widest distance between the iliopectineal lines. Difficult deliveries are defined as follows: (1) The biparietal diameter of the fetal head has not passed the inlet after a well-defined trial of labor, and cesarean section is done; (2) vaginal delivery has been accomplished, but the babies have had intracranial injury. All cases of elective cesarean section have been omitted as well as all sections for uterine inertia.

The Obstetrical Conjugate

Most authors agree that an obstetrical conjugate of 10.0 cm. is a borderline diameter. In this study (Fig. 1) it will be noted that the greatest break occurred at 10.5 cm., but there were difficult labors even when the obstetrical conjugate was over 11.5 cm. At the recommended border line there were difficult labors in 20 per cent of the cases, or only 1 in 5 patients, while above the border line there was difficulty in 4.2 per cent of the cases, or 1 in 25. In other words there is no assurance that above 10.0 cm. there will be no difficulty, and below it there is no assurance that there will be difficulty.

The Transverse Diameter

Our experience with the transverse diameter follows a similar pattern (Fig. 2). In this graph the same sort of picture is seen as with the obstetrical conjugate. Twelve centimeters are probably borderline. This break at 12.0 cm. appears to be even more pronounced than with the previous graph, but by itself is still not satisfactory. Note that at high levels or wide transverse

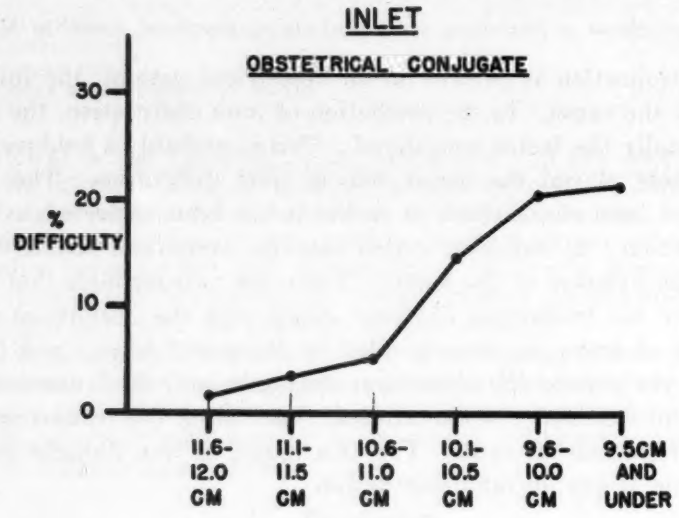

Fig. 1.

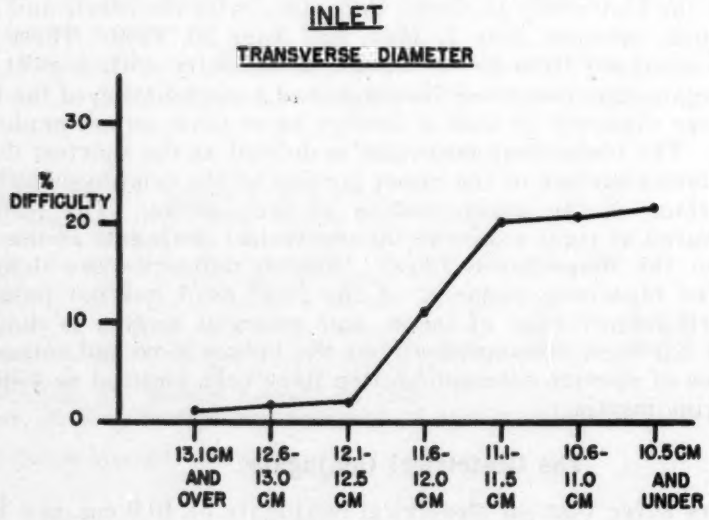

Fig. 2.

diameters (over 12.0 cm.) there was very little difficulty, 1.5 per cent, or 1 in 68 patients, while at lower levels (under 12.0 cm.), there was difficulty of 15.2 per cent, or about 1 in 7 patients. This spread of difficulty is moderately satisfactory for wide diameters, but when the narrow transverse diameters are used alone for prognosis it is not quite as good as the obstetrical conjugate, alone.

Obstetrical Conjugate and Transverse Diameter

The transverse diameter was considered as important as the obstetrical conjugate, and a scattergram was made (Fig. 3). Using various levels as borderline diameters, a borderline obstetrical conjugate of 10.0 cm. and a borderline transverse diameter of 12.0 cm. gave us the best results. Fig. 3, very simplified, shows the results of this method of treatment. When the obstetrical conjugate was over 10.0 cm. and the transverse diameter was over 12.0 cm., there was only 0.34 per cent difficulty, or 1 in 300. When the obstetrical conjugate was over 10.0 cm. but the transverse diameter was under 12.0 cm., there was 10.94 per cent difficulty, or 1 in 9 patients. This group emphasizes the importance of the transverse diameter and shows that it is of equal value with the obstetrical conjugate in predicting eutocia or dystocia.

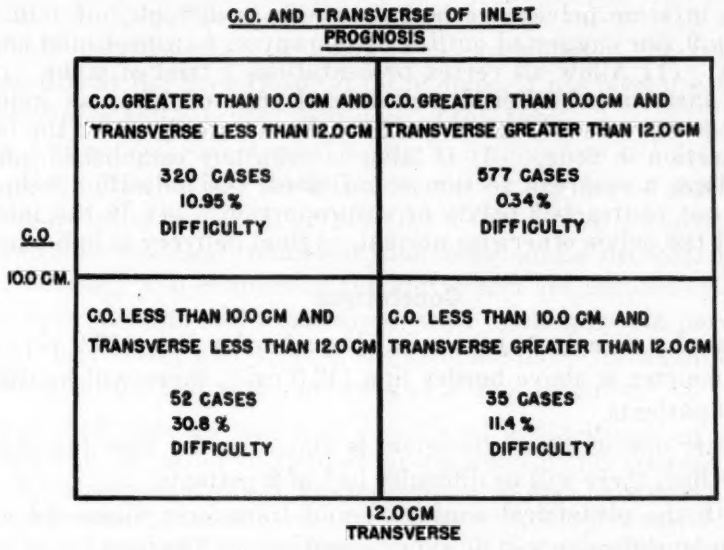

Fig. 3.

When the obstetrical conjugate is under 10.0 cm. and the transverse diameter is over 12.0 cm., there will be 11.49 per cent difficulty, again 1 in 9, or the same as when the obstetrical conjugate is more and the transverse is less than borderline. When the obstetrical conjugate is under 10.0 cm. and the transverse diameter under 12.0 cm., the difficulty increases to 31 per cent, or essentially 1 in 3 cases. Even though the number of patients with obstetrical conjugates under 10.0 cm. is limited, the results by statistical analysis are significant, and this could happen by chance only 1 in 1,000 times. In an attempt to find out if head size and weights played any role in this prognostic program, correlation was made in the various groups. Head size definitely did not play a role. This may very well be because of our inability to measure accurately and consistently biparietal and suboccipitobregmatic diameters either before or after delivery. Weight, surprisingly enough, was not significant. The patients who had difficult deliveries in the group in which the obstetrical conjugate was over 10.0 cm. and the transverse diameter under 12.0 cm. had babies of weights from 2,500 to 4,000 grams, the same range as with the easy deliveries. The same held true with the other quadrants of the graph (Fig. 3).

Comment

These observations show that the transverse diameter of the inlet is probably as important as the obstetrical conjugate in the determination of inlet

eutocia or dystocia. However, no one diameter at the inlet can receive more stress than another when prognosis is considered, and the relative length of each is the important factor. The simplicity of the method to determine inlet difficulty as outlined above may recommend itself for use. But the absolute prediction of inlet difficulty will not be obtained until one knows in any one patient the following: (1) accurate x-ray measurements, (2) exact inlet shape, (3) fetal position and the degree of head flexion at time of labor, (4) exact fetal head size and shape, and (5) the character of labor and the patient's soft tissue variations. The determination of the first three factors is moderately accurate. The evaluation of fetal head size and shape leaves something to be desired. The last factor, labor itself, the roentgenogram cannot evaluate. If labor is good, a moderately accurate prognosis can be given. If labor is poor or a uterine inertia type, prognosis is difficult.

Because in some pelves our best prognosis is difficulty of 1 in 3 and in others of 1 in 9, our suggested outline of therapy in a suspect inlet contraction is as follows: (1) Allow all vertex presentations a trial of labor. (2) If the inlet is not surmounted after a well-defined trial of labor as indicated by lateral roentgenograms with the biparietal diameter still above the inlet, then a cesarean section is done. (3) If labor is definitely established and uterine inertia develops, a cesarean section is indicated, the indication being uterine inertia and not contracted pelvis or disproportion. (4) If the inlet is surmounted and the pelvis otherwise normal, vaginal delivery is indicated.

Conclusions

1. If the obstetrical conjugate is above border line (10.0 cm.) and the transverse diameter is above border line (12.0 cm.), there will be difficulty in only 1 in 300 patients.

2. If either one of these diameters is above border line and the other is below border line, there will be difficulty in 1 of 9 patients.

3. If both the obstetrical conjugate and transverse diameters are below border line, inlet difficulty will be experienced in 1 of 3 patients.

References

1. Eastman: Williams Obstetrics, ed. 10, New York, 1950, D. Appleton-Century Company, Inc., p. 270.
2. Mengert, W. F.: J. A. M. A. **138**: 169, 1948.
3. Allen, E. P.: Brit. J. Radiol. **20**: 230, 1947.
4. Nicholson, C.: J. Obst. & Gynaec. Brit. Emp. **50**: 37, 1943.
5. Weinberg, A., and Scadron, S. J.: Am. J. Obst. & Gynec. **52**: 255, 1946.

RELATION OF LEUCOPLAKIC VULVITIS TO SQUAMOUS CARCINOMA OF THE VULVA

IVAN I. LANGLEY, M.D.,* ARTHUR T. HERTIG, M.D., AND GEORGE VAN S. SMITH, M.D., BROOKLINE, MASS.

(From the Clinic and Pathology Laboratories, Free Hospital for Women)

LEUCOPLAKIC vulvitis has been regarded since its earliest recognition as a precursor of squamous-cell carcinoma of the vulva.[1] In an attempt to correlate the relationship of squamous-cell carcinoma of the vulva and leucoplakic vulvitis at the Free Hospital for Women, it has been necessary to establish a reasonable and accepted definition of this term.

This was a histopathological study and therefore the following criteria were utilized. The corium shows a decrease or absence of elastic tissue (this elastic tissue being replaced by a collagenous deposit), marked decrease in glands and hair follicles, round-cell infiltration and a decrease in the number of blood vessels. The changes in the epithelium are divided into two phases: first, the hypertrophic and keratinized, with thickened rete pegs which reach down into the corium, and, second, the atrophic phase, in which the epithelium is thin, keratinized, and with shortened or absent rete pegs.

Leucoplakic vulvitis was first considered a nutritional or deficiency disease by Swift.[2] Hyams and Bloom,[3] proponents of this concept, treated their patients by a regime of dilute hydrochloric acid and parenteral and oral vitamin A, with some promising results. In a very comprehensive report, Miller and associates[4] studied the problem of leucoplakia vulvae in many ways. They approached the problem not only from the standpoint of age, symptoms, color, marital status, etc., but also on the basis of psychoneurosis, allergy, blood plasma vitamin A levels, gastric acidity, and hormonal assays. It should be noted that these factors could not be statistically correlated with the possible etiology of this disease. By the use of subcutaneous alcohol injections, Wilson[5] has demonstrated that patients with pruritus vulvae will in the majority of cases become symptom free. All patients in this author's study, in whom corium changes had been demonstrated, did, however, have a recurrence of their symptoms and progression of their disease.

There is no satisfactory clinical evidence that the dermis changes in leucoplakia can be improved by any type of therapy.[6]

Material and Findings

In this study the tissues from 208 vulvectomies done during the interval 1920 to 1950 were examined. In each instance tissue demonstrated the necessary characteristics of one or both phases of leucoplakic vulvitis. All other vulvar lesions were excluded.

Squamous-cell carcinoma was found concomitantly with leucoplakic vulvitis in 50 (24 per cent) of the 208 cases. In all but six of the 50 cases with carcinoma the hypertrophic phase of leucoplakia was present in some portion of

*Present address 1020 SW Taylor, Portland, Ore.

the lesion. The carcinoma of the remaining six cases (12 per cent) was associated with the atrophic phase.

In 158 cases in which leucoplakic vulvitis was the only diagnosis, simple or partial vulvectomy was performed. One hundred twenty-two of these 158 patients were followed for five years or longer, the longest follow-up being 18 years. Seventy-two (59 per cent) of the patients had recurrence of symptoms or lesions or both. Of these, only one developed squamous-cell carcinoma of the vulva 12 years after the first simple vulvectomy. Subsequent to the first operation, areas of leucoplakia were removed at 4, 5, and 7 years, respectively. Carcinomatous changes were noted only at the time of the fifth biopsy, 12 years following the first procedure. Subsequent to the diagnosis of carcinoma, a radical vulvectomy with bilateral groin dissection was performed. Eleven years later the patient still had leucoplakic vulvitis without any signs of persistence or recurrence of the carcinoma.

During this same thirty-year period (1920 to 1950) 32 cases of squamous-cell carcinoma without co-existing leucoplakic vulvitis were diagnosed and treated at the Free Hospital for Women. Fifty cases of carcinoma co-existed with leucoplakic vulvitis or 61 per cent of the total.

The average age of patients with leucoplakic vulvitis alone was 55.2 years, while the average age with carcinoma in addition was 66.8 years, an average of 11.6 years greater. The average age of patients with squamous-cell carcinoma without associated leucoplakic vulvitis was 57.1 years.

The average duration of symptoms for each of the groups were 4.85 years for leucoplakia alone, 3.24 years for associated carcinoma, and 1.69 years for squamous carcinoma alone.

TABLE I

PATHOLOGY	AGE (YEARS)	DURATION OF SYMPTOMS (YEARS)
Leucoplakic vulvitis	55.2	4.85
Leucoplakic vulvitis with carcinoma	66.8	3.24
Squamous-cell carcinoma	57.1	1.69

Comment

The number of cases of squamous-cell carcinoma of the vulva with concomitant leucoplakia agrees closely with the 70 per cent reported by Taussig.[7] Smith and Pollock[8] reported 36.4 per cent of all malignancies of the vulva to be associated with leucoplakia or 43.3 per cent of the cases of squamous-cell carcinoma with leucoplakia. Palmer[9] reported that 12 per cent of his cases had associated leucoplakia; however, 51 per cent of the patients had the chief complaint of pruritus vulvae. Eighteen per cent of the cases of carcinoma of the vulva had coexisting leucoplakia in a 62 per cent Negro study by Lunin.[10] Brown[11] cites 67 per cent with leucoplakic vulvitis. Miller and collaborators[4] reported 33 of 143 cases (23.1 per cent) of leucoplakia of the vulva associated with squamous-cell carcinoma.

The edema and trauma found with leucoplakia may make the clinical diagnosis of the disease difficult. Moreover, the clinical appearance of lichen planus, a neurodermatitis, Monilia vulvitis, and allergic dermatitis simulates leucoplakic vulvitis closely. This was emphasized by Miller and his associates.[4] These facts prove that a biopsy diagnosis should be made before the patient is treated.

Excision rather than conservative observation is warranted in all cases of leucoplakia.[8] While most leucoplakic vulvitis may not eventuate in

squamous-cell carcinoma, their co-existence is frequent enough to justify removing surgically all proved areas of leucoplakia.

The high recurrence rate following partial or simple vulvectomy (59 per cent) in patients followed over a five-year period would lead one to believe that inadequate surgery was performed. Careful microscopic examination of the surgical limits of the specimen removed would be an excellent guide to determine the extent of the disease. Doing such studies would encourage wider original excision or at least would predict the prognosis as far as recurrence is concerned.

Summary and Conclusions

Definite conclusions cannot be drawn from this study. Because of the presence of carcinoma in one out of every four patients having leucoplakic vulvitis, early and positive treatment is indicated.

Partial or simple vulvectomy was followed by a high percentage of recurrence in benign lesions.

Microscopic examination of the surgical limits of the specimen removed is recommended.

Radical vulvectomy with bilateral groin dissection is indicated in cases of carcinoma.

The average age difference of 11.6 years in patients with leucoplakic vulvitis alone and those with associated squamous-cell carcinoma may suggest that leucoplakic vulvitis is a premalignant disease.

References

1. Graves, W. P., and Smith, G. V. S.: J. A. M. A. **92**: 1244, 1929.
2. Swift, B. H.: M. J. Australia **2**: 541, 1932.
3. Hyams, M. N., and Bloom, O. H.: AM. J. OBST. & GYNEC. **53**: 214, 1947.
4. Miller, N. F., Parrott, M. H., Stryker, J., Riley, G. M., and Curtis, A. C.: AM. J. OBST. & GYNEC. **54**: 543, 1947.
5. Wilson, W. M.: West. J. Surg. **57**: 406, 1949.
6. Parks, J., and Martin, S.: AM. J. OBST. & GYNEC. **55**: 117, 1948.
7. Taussig, F. J.: AM. J. OBST. & GYNEC. **40**: 764, 1940.
8. Smith, F. R., and Pollock, R. S.: Surg., Gynec. & Obst. **84**: 78, 1947.
9. Palmer, J. R.: Surg., Gynec. & Obst. **88**: 435, 1949.
10. Lunin, A. B.: AM. J. OBST. & GYNEC. **57**: 742, 1949.
11. Brown, J. A.: Canad. M. A. J. **58**: 181, 1948.

EVALUATION OF TREATMENT FOR MONILIA IN PREGNANCY

HERMAN I. KANTOR, M.D., DALLAS, TEXAS

(From the Departments of Obstetrics and Gynecology of Parkland Hospital and Southwestern Medical Branch of the University of Texas)

THE symptoms resulting from mycotic infection of the vagina in the pregnant woman are frequently more severe than in the nonpregnant. Leucorrhea, pruritus, and a burning sensation of the vulva may become bitter complaints from which the patient demands relief. The changes which occur in the vagina during pregnancy are responsible for the severity of the symptoms, as well as for the increased incidence of infection.

Bland, Rakoff, and Pincus[1] inoculated experimentally the vaginas of pregnant and nonpregnant women with Monilia. Their material was obtained from patients with monilial vulvovaginitis and from newborn babies with oral thrush. They reported the development of infection in approximately 80 per cent of the pregnant but only 30 per cent of the nonpregnant women.

What are the changes which render the vagina so susceptible to infection during pregnancy? A review of the investigations already carried out offers an acceptable explanation. In 1934, Hesseltine, Borts, and Plass[2] proved that the fungi of Monilia may cause vaginal and vulval infection. These organisms grow best in the presence of sugars and in an acid medium. Cruickshank and Sharman[3] state, "As pregnancy advances, an increase in the glycogen content of the vaginal mucous membrane occurs." The Döderlein bacillus causes the fermentation of glycogen, producing lactic acid. Since the best environment is thus provided, the vagina in pregnancy becomes an ideal culture medium for Monilia. Moreover, for these same reasons the infection is rendered less susceptible to treatment. Even the time-honored gentian violet, so difficult to apply correctly by the patient, and so undesirable because of staining and reactions, frequently fails.

In 1947, Alter, Jones, and Carter[4] suggested treatment with propionate vaginal jelly, which could be easily self-administered, and did not have the objectionable staining of the dyes. Their preliminary report indicated no sensitivity reactions.

In view of these encouraging results, it seemed advisable to evaluate further the response to treatment with this preparation. Since culture represents the most accurate method for the diagnosis of Monilia, this procedure, as well as the subjective relief from symptoms, was used in this study.

Material and Methods

Cultures were taken from the vaginas of patients at the initial visit to the prenatal clinic of Parkland Hospital. These were inoculated without delay on freshly prepared Sabouraud's medium. Our laboratory reports these cultures as "no growth," or "light" "moderate," or "heavy growth."

Seventy-two patients in whom Monilia was found were chosen for this investigation. Twenty-nine served as a control group, and received no treatment of any kind. The others were treated, and, when possible, follow-up cul-

tures were taken after treatment, and six weeks after delivery. Patients were questioned carefully regarding symptoms before treatment was instituted and again three or four weeks after completion.

Treatment consisted of the vaginal instillation of one-half to three-fourths of an applicatorful of propionate jelly* nightly. The lesser amount was advised when the patient complained that the jelly "ran out" during the night. Also, an additional instillation was advised prior to intercourse, with the hope that reinfection might be curtailed.

The patients were requested to continue this treatment for at least two and preferably three weeks. It was considered safe to start treatment through the thirtieth week of the pregnancy. Beyond this time, symptoms were treated by external application alone, and these patients are not included in this study. However, many said they did experience marked relief.

Results

Occasional complaints were offered that "the treatment was messy." For the most part, these came from patients in whom symptoms were minimal or absent. A reduction in the quantity of jelly used generally made the treatment more acceptable. Among patients with severe irritation, the welcome relief more than compensated for the "annoyance."

Careful questioning led us to believe that most of the patients faithfully carried out the prescribed course. There were no manifestations of allergy or poor tolerance of the jelly. Several patients in whom the primary infection of the vulva was severe complained of a transient burning sensation. However, they were willing and anxious to continue the treatment.

At the time of the visit six weeks post partum, the cultures from 28 of the 29 control patients were negative, and 1 showed light growth (Table I). As indicated previously, these patients were not given any specific treatment.

TABLE I. CONTROL PATIENTS

FIRST CULTURE REPORT	NUMBER	6 WEEKS AFTER DELIVERY
Light growth	2	No growth
Moderate growth	8	No growth
Heavy growth	19	18 No growth
		1 Light growth
Total	29	28 No growth
		1 Light growth

Their symptoms, when present, were fairly persistent. However, their mycotic infections disappeared spontaneously after the pregnancy terminated. Culture follow-up cannot be used, therefore, as a measure of the efficacy of treatment during pregnancy.

Among 43 patients scheduled for treatment, only 9 were asymptomatic (Table II). Discharge was the most prominent symptom, and itching was present in approximately one-half. There was no relationship between the "heaviness" of the culture growth and the severity of symptoms.

TABLE II. TREATED PATIENTS, SYMPTOMS

CULTURE REPORT	NUMBER	DISCHARGE	ITCHING OR BURNING	NO SYMPTOMS
Light	8	7	5	1
Moderate	2	2	1	0
Heavy	33	24	18	8
Total	43	33	24	9

*The propionate jelly (Propion-Gel) was supplied by Wyeth Incorporated.

Use of the propionate jelly exactly as prescribed was carried out by 38 patients (Table III). Of these, 29 showed improvement, usually quite prompt. Seven could see no change, and 2 considered their symptoms worse.

TABLE III. RESPONSE TO TREATMENT

SYMPTOMS	NUMBER	CULTURE 6 WEEKS AFTER STARTING TREATMENT			CULTURE 6 WEEKS AFTER DELIVERY		
		POSITIVE	NEGATIVE	NONE OBTAINED	POSITIVE	NEGATIVE	NONE OBTAINED
Improved	29	17	10	2	1	18	10
No change	7	2	3	2	2	5	1
Worse	2	0	2	0	0	2	0
Total	38	19	15	4	3	25	11

There was little correlation between the change in symptoms and the report of the cultures taken six weeks after starting treatment, three or four weeks after completion. Of the 29 patients who stated their symptoms were improved, for example, 17 still had positive cultures. On the other hand, both of the patients who thought their symptoms were worse had negative cultures after treatment.

Several explanations may be offered for this apparent inconsistency:

1. The vaginal environment, altered by treatment, may inhibit the spread of the infection. Although symptomatic improvement may follow, the culture may remain positive.
2. The occurrence of reinfection is difficult to detect.
3. Symptoms produced by monilial vulvovaginitis are not specific.
4. The psychogenic value of this or any form of treatment must be considered. However, its role in the face of persistent symptomatic improvement seems minor.

In this series, 15 of 34 patients in whom completed reports were obtained had negative cultures six weeks after starting vaginal treatment. As with the control series, nearly all of the patients had negative cultures six weeks after delivery.

Conclusions

1. Propionate jelly is a satisfactory and relatively easy method for treating monilial infection of the vulva and vagina during pregnancy.
2. Improvement in symptoms may be anticipated in approximately 75 per cent of patients.
3. Culture from the vagina taken six weeks after the propionate jelly treatment was started became negative in almost 45 per cent of the patients.
4. There were no ill effects resulting from this treatment.
5. Among pregnant patients with positive cultures for Monilia, repeat cultures six weeks after delivery will be negative in more than 90 per cent of patients, even if no treatment is given.

I should like to record my appreciation to Dr. W. F. Mengert for his advice in preparing this manuscript and to Mrs. C. Green for her technical assistance.

References

1. Bland, P. B., Rakoff, A. E., and Pincus, I. J.: Arch. Dermat. & Syph. 36: 760, 1937.
2. Hesseltine, H. C., Borts, I. C., and Plass, E. D.: AM. J. OBST. & GYNEC. 27: 112, 1934.
3. Cruickshank, R., and Sharman, A.: J. Obst. & Gynaec. Brit. Emp. 41: 369, 1934.
4. Alter, R. L., Jones, C. P., and Carter, B.: AM. J. OBST. & GYNEC. 53: 241, 1947.

3534 MAPLE AVENUE

THE USE OF AUREOMYCIN IN OBSTETRICS AND GYNECOLOGY*

H. CLOSE HESSELTINE, M.D., AND H. D. PRIDDLE, M.D.,** CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-in Hospital)

THE mortality incidence caused by infections in obstetrical and gynecological patients has been greatly diminished during the last decade, in part due to improved technique, adequate pre-, intra-, and postnatal, pre- and postoperative care, fluid balance and blood replacement measures. What was once the most common cause of death in the puerperium has now been relegated to a position below heart disease, toxemia, and hemorrhage as the cause of death in obstetrics. Operative obstetrical and gynecological morbidity has also been markedly reduced at a similar rate, because of the above-mentioned improvements with the addition of therapeutic drugs which are bactericidal for the majority of organisms encountered in this field of medicine. Sulfonamides first aided the obstetrician and gynecologist to lower morbidity; these were followed by penicillin, streptomycin, and now aureomycin, terramycin, and Chloromycetin.

All of the above drugs have had, or are being given clinical trial in the field of infections of the female genital tract. These studies carried on in many institutions have altered our use of chemotherapeutic drugs to specific drugs for the offending organism, thereby reducing the patient hospital days to a minimum and bringing about a more rapid recovery. Hospital facilities are at a premium, and any form of therapy which can and will shorten safely the hospital stay is very desirable.

We became interested in the use of aureomycin as a prophylactic drug against cystitis and pyelitis as a result of catheterizations or trauma of indwelling cathethers in the postpartum and postoperative care of the bladder. Retention and other faults of bladder function are common complications in obstetric and gynecologic patients. The use of retention catheters continues to be a routine procedure in many types of postoperative gynecologic patients; therefore, prophylaxis is necessary as infections are common complications without urinary antisepsis.

The literature on this new antibiotic (aureomycin) is already voluminous. Aureomycin does fill a needed gap in the therapeutic armamentarium for certain organisms unaffected by penicillin and streptomycin. It is very effective against most of the types of bacteria which cause infections in the urinary tract, is nontoxic, and effective urinary concentration can be established by

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**Present address, Wayne University, Detroit, Mich.

oral administration. Collins and associates[1] found that, after a single dose of 0.5-0.75 Gm. of aureomycin given to a normal fasting patient, the antibiotic was recovered in the urine for more than 33 to 55 hours. The largest rate of excretion was between 2 and 8 hours; thus they recommended dosage intervals of 8 hours. These same authors found that most organisms were inhibited by 6.3-50 micrograms per milliliter excepting Proteus and Pseudomonas. These were approximately the results of Carroll and Allen.[3] Rutenburg[4] in making in vitro studies concluded that aureomycin was effective against many gram-negative bacilli, but the sensitivity of various strains of given species varied greatly.

Formerly, sulfathiazole in 0.5 Gm. amounts four times daily (total of 2 Gm. per 24 hours) was very effective prophylactically; nevertheless, complications of sensitization occurred occasionally. It was elected to avoid all sulfonamides but to use oral therapy. Aureomycin was available and was given a trial.

Material

The group in which there was the problem of prophylaxis against cystitis and pyelitis from an indwelling catheter or repeated catheterization consisted of 112 patients, of whom 39 were obstetric and 73 gynecologic. Routinely, residual determinations were made on all patients after the removal of catheters or, in instances of urinary retention, until there were two consecutive residual urine specimens of 100 c.c. or less. Sedatives and medication were continued during this period.

The gynecologic group had as an average 5 days of retention catheterization. The majority of these were patients who had vaginal plastic repair or major abdominal surgery (total hysterectomy). The average duration for the obstetric group was 3 days. Inasmuch as the majority of this group were patients who were unable to urinate after delivery, the routine was the insertion of a Foley catheter for 48 to 72 hours; therefore, the average days of retention catheter were much less.

In addition to the summation of the prophylactic value of aureomycin, reports are included on three cases of urinary tract infection, three cases of intrapartum fever, two cases of endometritis, and one case of pelvic peritonitis treated with aureomycin.

The regular urinalysis of these patients consists of albumin and reduction tests, and microscopy for degree of pyuria and type of bacteria present. White blood counts are also made regularly.

Dosage

The report of Herrell[5] indicates that during the administration of multiple doses of aureomycin the urinary concentration of aureomycin far exceeds the amount necessary to inhibit the growth of microorganisms frequently found in the genitourinary system; thus, for prophylaxis, we arbitrarily chose a total of 1 Gm. daily given in four units of 250 mg. at six-hour intervals. This aureomycin therapy was started the day after surgery and in other patients on the day of insertion of the retention catheter. The dose was maintained until such time as the catheterizations were discontinued.

The treatment of endometritis and urinary tract infection was with 0.5 Gm. four times daily or a total of 2 Gm. daily, while the intrapartum fever cases were treated with but 1 Gm. daily in four equally divided doses.

Results

The group of 112 patients tolerated the oral administration of aureomycin very well with the exception of five patients who had nausea and/or vomiting. In two of these the nausea and vomiting were severe enough to necessitate discontinuance of the aureomycin. The questionable efficacy of aluminum acetate hydroxide in the alleviation of these symptoms and the problem of oral administration and tolerance in the early postoperative period weighed against its use. Two patients had hyperactivity of the bowel which was easily controlled when the aureomycin was discontinued. Diarrhea was present in 25 per cent of Carroll's series, while our incidence is only 1.8 per cent.

The regular (microscopic) examination of catheterized specimens revealed that the urine (uncentrifuged specimens) remained free of leucocytes in all but nine cases. Four of these had less than 5 white blood cells per high-power field. The five remaining had definite pyuria. In two this was present during aureomycin therapy, while, in the three remaining, pyuria occurred after prophylaxis ceased. These patients had no urinary symptoms and were given no other therapy, as the urine cleared quickly with the increase of fluid intake. If we include all the above cases we have a failure rate of 8 per cent for prophylaxis of cystitis with aureomycin.

The leucocyte counts ranged from 5,300 to 21,000 per cubic millimeter, with no definite trend toward either leucopenia or leucocytosis. The leucocytosis was evidently the result of infection outside the urinary tract, except when the infection was there before institution of therapy.

The three patients with urinary infection treated with aureomycin became symptom free and with negative microscopic urinalysis 3, 3, and 9 days, respectively, after institution of therapy. In two of these cases *Escherichia coli* was cultured from the urine, which was resistant to adequate therapeutic doses of streptomycin. One patient had received both sulfathiazole and streptomycin in therapeutic doses without a cure. The dose of the aureomycin given was 2 Gm. daily in four equally divided doses (500 mg. four times daily).

Intrapartum fever was treated with 2 Gm. aureomycin daily for five days, and all these patients were afebrile the day after delivery, which is not conclusive evidence that aureomycin affected the course in any way. Guilbeau and associates[6] report excellent results in reducing the incidence of endometritis by the use of aureomycin prophylactically in patients during labor and two to three days post partum.

In two cases of endometritis treated with 2 Gm. daily, both patients became afebrile after four days of therapy, but the response seemed slower than that commonly encountered when penicillin is the therapeutic agent for endometritis. However, two cases are not enough to warrant a definite conclusive opinion.

The case of pelvic peritonitis after laparotrachelotomy will be summarized briefly:

E. R., No. 481100. The patient was a primigravida, admitted to the hospital at 37 weeks' gestation because of ruptured membranes and bright red vaginal bleeding. Vaginal examination was done without palpation of the placenta and with a diagnosis of mild partial abruptio placentae resulting. Twenty-four hours lapsed after the membranes ruptured without the onset of active labor. At this time a laparotrachelotomy was performed under spinal anesthesia with the delivery of a normal 2,280-gram female infant. There was an old 150-c.c. clot adherent to the placenta.

The next morning, the temperature was 39.7° C., the pulse was 144, and the leucocyte count was 14,500. The patient had two severe chills and moderate abdominal distention had become apparent. Blood cultures at this time remained negative. The patient was

given intravenously 400 mg. of aureomycin dissolved in normal saline immediately, and 200 mg. four and eight hours later, and twelve hours after the initial dose 400 mg. were given again (a total of 1.2 Gm. in 12 hours). This amount of aureomycin was given daily for four more days with little improvement in the patient's condition. The temperature continued to be above 39° C., pulse over 100, along with elevated leucocyte count. Then, after five days of intravenous aureomycin therapy, the patient was given penicillin and streptomycin and 18 hours later was afebrile. Pelvic examination on the fifth day after surgery revealed fullness, tendernes, and pain on palpation on the left side. The patient received adequate aureomycin intravenously as described, but, seemingly, an organism was present that was resistant to this chemotherapeutic drug.

Brainerd[7] reported that the intravenous administration of aureomycin gives a high concentration of the drug in five minutes and the serum level decreases rapidly the first hour and slowly thereafter for six hours. Herrell states that 2 to 4 micrograms of serum aureomycin is an effective concentration, and that effective therapeutic level may be found in the serum 12 hours after the administration of 0.5 Gm. intravenously.

Summary

1. Aureomycin proved effective in the prevention of cystitis resulting from retention catheters or repeated catheterizations in 92 per cent of 112 cases.

2. Intrapartum fever and endometritis may be treated with aureomycin but, in our hands, penicillin is the chemotherapeutic drug of choice.

3. Aureomycin is a desirable chemotherapeutic agent for treatment of most urinary tract infections occurring in the obstetric and gynecologic patient.

4. A case of peritonitis treated unsuccessfully with intravenous aureomycin is described.

The authors thank Lederle Laboratories Division, American Cyanamid Company, for the contributions of aureomycin used in this study.

References

1. Collins, H. S., Wells, E. B., Paine, T. F., Jr., and Finland, M.: Proc. Soc. Exper. Biol. & Med. 69: 174, 1948.
2. Collins, H. S., and Finland, M.: Surg., Gynec. & Obst. 89: 43, 1949.
3. Carroll, G., Allen, H. N., and Flynn, H.: J. Urol. 62: 574, 1949.
4. Rutenburg, A. M., and Schweinburg, F. B.: Proc. Soc. Exper. Biol. & Med. 70: 464, 1949.
5. Herrell, W. E., and Heilman, F. R.: Proc. Staff Meet. Mayo Clin. 24: 157, 1949; 24: 612, 1949.
6. Guilbeau, J. A., Jr., Schoenbach, E. B., Schaub, I. G., and Latham, D. V.: J. A. M. A. 143: 520, 1950.
7. Brainerd, H. D., Bruyn, H. B., Jr., Meiklejohn, G., and Scaparone, M.: Proc. Soc. Exper. Biol. & Med. 70: 318, 1949.

MATERNAL MORTALITY AT MILWAUKEE HOSPITAL*

F. J. Hofmeister, M.D., and J. G. Stouffer, M.D., Milwaukee, Wis.

A STUDY has been made at the Milwaukee Hospital in an attempt to analyze the etiology of maternal deaths.

During the sixteen-year period from 1934 to 1949 there were 25,019 deliveries with 22 maternal deaths at the Milwaukee Hospital. All deliveries were of private patients under the care of general practitioners, who delivered 29 per cent in 1949, while specialists cared for the remaining 71 per cent. The maternal mortality rate for the period was 0.087 per cent.

These sixteen years have been divided into four-year periods for the purpose of comparison. The progressive downward trend of the maternal mortality rate is shown in Table I, with 0.27 per cent for the first period as compared with 0.037 per cent in the last period. This is a most significant and satisfactory trend.

Table I

YEARS	NUMBER OF DELIVERIES	MATERNAL DEATHS	MORTALITY RATE (%)
1934-1937	3,258	9	0.276
1938-1941	3,816	4	0.105
1942-1945	7,206	5	0.069
1946-1949	10,739	4	0.037

In order to determine what was happening in the city of Milwaukee and the state of Wisconsin, a statistical comparison was made of their maternal mortality rates. It is gratifying to note that a similar trend is pronounced throughout the entire state. Comparative rates are shown in Table II.

Table II. Material Deaths per 1,000 Live Births

YEARS	MILWAUKEE HOSPITAL	CITY OF MILWAUKEE	STATE OF WISCONSIN
1934-1937	2.76	3.6	3.82
1938-1941	1.05	2.5	2.74
1942-1945	0.69	2.03	1.72
1946-1949	0.37	1.1	0.99*

*Provisional figure.

The causes of death are grouped under Infection, Toxemia, Hemorrhage, and Miscellaneous in Table III. It has been commonly stated that 85 per cent of maternal deaths are due to the triad of infection, toxemia, and hemorrhage. At least in our hands this is no longer true. Table III shows that over one-third of the deaths were due to miscellaneous causes. In the last four-year period one-half of the deaths were classified under this heading. Douglas, in a similar study, states, "Our experience in recent years indicates that maternal deaths have resulted largely from diseases of the cardiovascular system and malignant tumors rather than from obstetrical causes." The mortality rate as given by Douglas was 1.5 per cent per 1,000 pregnancies. From Margaret Hague Maternity Hospital a somewhat similar report has been made for the

*Presented before the 612th regular meeting of the Chicago Gynecological Society, Dec. 15, 1950.

year 1949. They report their first hemorrhage death in years in a case of abdominal pregnancy. In the entire sixteen-year period of our series, 36.4 per cent of the deaths were due to infection, 18.6 per cent to toxemia, and 9.1 per cent to hemorrhage.

TABLE III. CAUSES OF MATERNAL DEATHS

I. Infection—8, or 36.4 per cent
A. Genital—5
1. Septicemia and generalized peritonitis following cesarean section—4
2. Peritonitis following version and extraction—1
B. Extragenital—3
1. Pneumonia following cesarean section—1
2. Seven months' pregnancy with mastoiditis and septicemia—1
3. Acute bacterial endocarditis with lung abscess—1
II. Toxemia—4, or 18.1 per cent
A. Eclampsia with cerebral hemorrhage—1
B. Eclampsia with uremia—2
C. Malignant hypertension with uremia following cesareon section—1
III. Hemorrhage—2, or 9.1 per cent
A. Postpartum hemorrhage with anuria—1
B. Postoperative hemorrhage with uterine apoplexy following cesarean section—1
IV. Miscellaneous—8, or 36.4 per cent
A. Pulmonary embolism—2
B. Caudal anesthesia reaction—2
C. Congestive heart failure—2
D. Abdominal pregnancy—1
E. Inverted uterus—1

Seven of the 22 deaths, or 32 per cent, were associated with cesarean section. During the past sixteen years there have been 1,510 cesarean sections performed on these 25,019 patients, an incidence of 6 per cent. The maternal mortality rate for this operation was 0.46 per cent. All of these deaths occurred prior to 1940. It is noteworthy that since that time there have been 1,128 consecutive cesarean sections with no maternal deaths. None of these operations was of the extraperitoneal type. The causes of death following cesarean section are shown in Table IV. Five of the seven were due to infection, and all of them occurred before the advent of antibiotic and sulfonamide therapy.

TABLE IV. MATERNAL DEATHS FOLLOWING CESAREAN SECTION

Septicemia and generalized peritonitis	4
Postoperative bronchopneumonia	1
Malignant hypertension, uremia	1
Postoperative hemorrhage, uterine apoplexy	1

The maternal deaths are further analyzed in Table V where they are again grouped into four-year periods. The decrease in deaths from infection is most striking, with all but one death having occurred before 1942. This one death might be classified as miscellaneous, having been due to acute bacterial endocarditis resulting from an overwhelming staphylococcus septicemia with a penicillin-sulfonamide resistant organism. The role of the sulfonamides and antibiotics is conceded to be one of the greatest factors in eliminating infection as a cause of maternal death.

During the entire sixteen-year period there were four deaths (18.1 per cent) from toxemia of pregnancy. Three of these were due to eclampsia, and the fourth was due to malignant hypertension with uremia. It would appear from Table V that toxemia is increasing as a cause of maternal mortality; however, the relative increase in the number of deliveries supersedes that, so death

from toxemia is actually decreasing. Nevertheless, toxemia still exists as a constant threat to maternal life. Improved prenatal care more than any other factor has been responsible for the reduction in the incidence of toxemia. All patients with toxemia are individually appraised and treated with some modification of the Stroganoff regime. This briefly consists in sedation, salt-poor high-protein diet, ammonium chloride, and careful observation. If the toxemia does not respond to medical treatment, early induction of labor is attempted and vaginal delivery anticipated. Cesarean section is reserved only for treatment-resistant cases in the nonconvulsive state. A recent survey of our sections showed that from 6 to 8 per cent of these operations were performed because of toxemia.

Two deaths were directly attributable to hemorrhage. One was the result of anemia following postpartum hemorrhage. In retrospect it appears that, instead, this was a case of lower nephron nephrosis and should not be classified as hemorrhage. The other death resulted from postoperative bleeding following a cesarean section done for uterine apoplexy. Although a hysterectomy was performed as a lifesaving measure, the exsanguination was too great. Both of these cases occurred in 1935, a period prior to the establishment of the blood bank. Whole blood is now readily available at all times to combat this emergency. This, plus the use of plasma, red cell mass, and parenteral fluids were the greatest factors in the elimination of death due to hemorrhage.

Among the miscellaneous causes of death, which, as a group, continue to show a relative increase, there were two cases of postpartum pulmonary embolism. Both of these followed vaginal delivery and occurred during the earlier years. There were no deaths from pulmonary embolism after 1939. At that time early ambulation was instituted and has been supplemented by a more intensive therapy. Thrombophlebitis and phlebothrombosis are treated with Dicumarol, heparin, and by venous ligation.

Two deaths occurred in the period 1942 to 1945 from caudal anesthesia. Both deaths were credited to errors in administration of the anesthetic agent. It was during this time that caudal anesthesia enjoyed tremendous popularity at this institution. Since then, saddle block or some type of local anesthesia has been used in addition to the time-proved general inhalation anesthesia. There were no deaths attributable to any type of anesthesia other than caudal.

Two deaths were the result of congestive heart failure. One was from cardiac failure with severe rheumatic heart disease and the other from a decompensation during labor.

One death was from irreversible shock suddenly appearing six hours after an uneventful spontaneous delivery. The patient did not bleed excessively but suddenly showed evidence of severe and profound shock. There was no response to supportive therapy, blood, oxygen and various stimulants. Although the autopsy showed an inverted uterus, there were no symptoms of this complication. It is our opinion that this case should be classified as an avoidable death. A few of us believe that every cervix should be inspected immediately

TABLE V

CAUSE OF DEATH	1934-1937	1938-1941	1942-1945	1946-1949
Infection	5	2	0	1
Toxemia	1	0	2	1
Hemorrhage	2	0	0	0
Miscellaneous:				
Pulmonary embolism	1	1	0	0
Caudal anesthesia reaction	0	0	2	0
Congestive heart failure	0	1	0	1
Inverted uterus	0	0	1	0
Abdominal pregnancy	0	0	0	1

after delivery of the placenta and before the repair of the episiotomy. Lacerations of the cervix could be detected and repaired and such incidental findings as an inverted uterus discovered and corrected and a life probably saved.

One death, the most recent one (1948), occurred in a patient who was diagnosed as having a full-term abdominal pregnancy. She was a very obese multigravida. A laparotomy was performed to deliver a normal living infant. The placenta was left in situ. Her convalescence was relatively uneventful for this type of procedure. She was ambulatory for ten days and suddenly expired on the twenty-fifth postoperative day while using the bedpan. Clinically, the cause of death was typical of embolism, but an incomplete autopsy did not reveal a fatal embolic process below the head and neck. The pathological diagnosis was hepatic insufficiency.

Comment and Conclusions

This study deals with deaths per 1,000 livebirths. However, the statistics in the case of the Milwaukee Hospital refer only to pregnancies advanced beyond the fourth month. They do not include ectopic pregnancies or abortions. Since there were no deaths associated with abortion or ectopic pregnancy, the death rate, as customarily reported from the Bureau of Vital Statistics, is, in

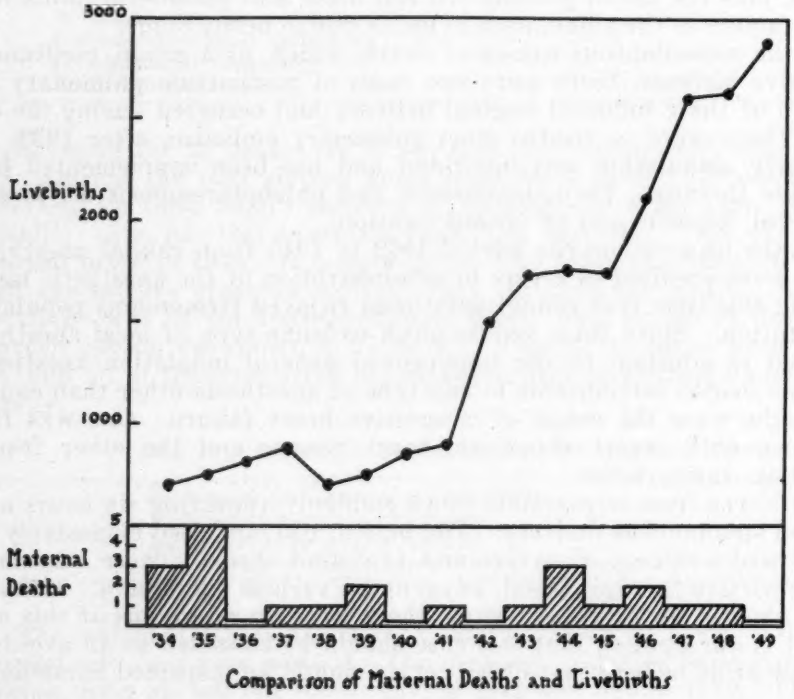


Fig. 1.

the case of Milwaukee Hospital (0.037 per cent), actually lower than shown in the earlier part of this paper. It is apparent that our maternal mortality is progressively approaching an irreducible minimum. (Fig. 1.). There were two deaths in the last 8,400 deliveries. It is no longer true that infection, toxemia, and hemorrhage cause 85 per cent of the maternal deaths. We find that hemorrhage and infection have been practically eliminated as causes of death in this institution during recent years. Four factors contributed to this reduction. The first has been a better attitude toward obstetrics and the han-

dling of obstetrical problems by the general practitioner. This is the result of improved methods of teaching undergraduates. Today the preclinical instruction has been most thoroughly integrated with an abundance of clinical experience. Undergraduates, interns, residents, and general practitioners are exposed to frequent staff conferences where not only newer methods of obstetrical practice are described, but our diagnostic shortcomings and morbidities are fully discussed. Second, the general practitioner and specialist alike have, year after year, become more meticulous and exacting in their prenatal care. This has included proper diet instructions, prenatal blood counts, typing, Rh determination, and routine chest x-rays. Third, there were fewer neglected and mismanaged cases. This was the result of a unique practice in vogue for many years whereby any general practitioner or specialist in Milwaukee Hospital has been able to obtain consultation or actual operative assistance from a member of the staff without any additional charge to the patient. Cesarean sections are all performed by certified obstetricians and here again no primary section can be performed without consultation with a member of the staff. Fourth, the presence of a constant supply of blood available for immediate use, on a generation of patients who no longer fear transfusions or the events of pregnancy, together with the advent of miraculous chemotherapeutic and antibiotic agents have been deciding factors in the elimination of many of the fatalities from obstetrics.

Some of these four fundamental factors are likewise responsible for a reduction in the incidence of death from toxemia. In the near future this may be stricken from the list of leading causes of death in this and all other institutions.

Even though all of these fundamental factors are observed, deaths do occur. These are primarily the result of diseases of the mother coincidental to pregnancy. The words, "primarily the result of diseases of the mother," should be emphasized, for this means that with early detection and successful treatment of these conditions, still further reduction of fatalities will result. Let us advocate thorough and more conscientious prenatal examinations and better prenatal care.

In conclusion, there is no better admonition than that of Dr. Amy Hunter, chief of the Department of Maternal Welfare of the State of Wisconsin, who states that although she is proud of the decreased maternal death rate in our state (.06 per cent in 1949), she shudders lest complacency result in carelessness, and sudden upswings occur in the death rate.

References

1. Verch, L. H., Stouffer, J. G., and Cron, R. S.: Am. J. Obst. & Gynec. 59: 108, 1950.
2. Douglas, R. G.: 151st Annual Report of the Society of the Lying-in Hospital of the City of New York.
3. Chesley, L. C.: Bull. Margaret Hague Maternity Hosp. 3: 24, 1950.
4. Spademan, L. C., and Heath, L. P.: Harper Hosp. Bull. 5: 97, 1947.
5. Krumbiegel, E. R.: Personal Communication.
6. Hunter, Amy: Personal communication.
7. Davis, M.: Personal communication.
8. Evans, S.: Personal communication.
9. Shutter, H.: Personal communication.

9028 W. Wright Street, Wauwatosa, Wis.

Discussion

DR. M. EDWARD DAVIS.—Maternal mortality has continued to decrease each year in the United States so that it has reached the surprising figure of less than one per thousand live births in 1949. This phenomenal record has surpassed the fondest predictions of

that group of obstetricians who embarked on a program to reduce the hazards of childbirth more than fifteen years ago. Obviously, the low point has not been reached, for if we could provide the same safeguards in maternity care for all of our people that we now provide for more than 85 per cent of our population, the present mortality rate could be halved.

The splendid report from a large private hospital is an example of what can be accomplished in our well-organized institutions. Deaths from the three major causes of maternal mortality have practically disappeared. However, hemorrhage, toxemias, and infection still account for more than 90 per cent of the deaths in the country at large. Obviously, we already possess the knowledge to prevent most of these fatalities.

The data which I present this evening from the Chicago Lying-in Hospital are quite similar to that from the Milwaukee Hospital. They confirm the observation that heart disease, thrombosis and embolism, and complications accidental to pregnancy account for most deaths in well-organized institutions. Heart disease has loomed more important as a cause of maternal mortality with the ever decreasing mortality rate. In more than 90 per cent of cardiac patients seen during pregnancy, the complication is rheumatic in origin. The prevention of deaths from heart failure in pregnancy and labor is primarily a problem of the prevention and care of rheumatic fever. New medical knowledge may soon have a major impact on this disease. In the meantime, the obstetrician must give greater emphasis to the care of the cardiac patient. Our present obstetrical management may have to be altered in that we may have to adopt a more radical approach. Certainly it is no achievement to bring orphans into the world nor do the rewards of pregnancy justify the great hazard involved in some patients.

Thrombosis and embolism are the most frequent causes of mortality in large maternities. The management of this complication has not become uniform. The value of vein ligation and anticoagulants is still being assessed. However, anticoagulant therapy has much appeal in pregnancy complications. The altered blood physiology as well as physical changes induced in veins by alterations in their walls and abnormal external pressures favor phlebothrombosis. In spite of the vagaries of anticoagulants, their more widespread and intelligent use should be rewarding.

What has brought about the splendid results which we report so enthusiastically? Increased hospitalization of maternity patients has been a major factor. The hospital has provided the manifold safeguards of modern medicine. It has made possible the availability of trained personnel at all times and for all patients. The advances of medicine and surgery have had a tremendous impact on obstetrics, but equally important is improved education for doctors who deliver the babies.

Studies such as Dr. Hofmeister presented should not represent dull statistics, but they should provide food for thought. How can we continue to decrease deaths in childbirth and, what is more important, the reparable and irreparable damage that cannot be tabulated? I have indicated one way, by providing the same maternity safeguards for the 15 per cent of our mothers who do not now enjoy the benefits available to the majority. Increased emphasis on lay education will result in more intelligent and cooperative patients, happier mothers, and fewer obstetrical hazards. New scientific knowledge must accrue to the benefit of obstetrics as well as to all medical care. Although the rewards of progress in

TABLE I. MATERNAL MORTALITY AT CHICAGO LYING-IN HOSPITAL
1944 TO 1950

DATES	DELIVERIES	DEATHS	RATE PER 1,000 BIRTHS
July 1, 1944 to July 1, 1945	3,471	0	0
July 1, 1945 to July 1, 1946	3,533	1	0.35
July 1, 1946 to July 1, 1947	4,108	3	0.73
July 1, 1947 to July 1, 1948	4,006	0	0
July 1, 1948 to July 1, 1949	4,089	2	0.49
July 1, 1949 to July 1, 1950	3,874	2	0.52
July 1, 1944 to July 1, 1950	23,081	8	0.34

the future will not be as spectacular as they have been in the past fifteen years, we still have not reached that point where the law of diminishing returns begins to operate. In fact, the rewards in happier, healthier mothers and babies may well prove to be a greater achievement than the saving of barren lives.

TABLE II. CAUSES OF MATERNAL MORTALITY CHICAGO LYING-IN HOSPITAL 1944 TO 1950

NAME	DATE	DURATION OF PREGNANCY	DELIVERY	CAUSE OF DEATH		PREVENTABLE FACTORS
				OBSTETRICAL	NONOBSTETRICAL	
Mrs. Tu	1945	30 weeks	Undelivered		Scleroderma	No
Mrs. F	1946	24 weeks	Natural		Biliary cirrhosis	No
Mrs. P	1947	27 weeks	Undelivered		Thrombosis embolism	No
Mrs. Mc	1947	Term	Outlet forceps	Thrombosis, embolism		Yes
Mrs. Tau	1948	36 weeks	Cesarean section	Thrombosis, embolism, toxemia		Yes
Mrs. B	1949	14 weeks	Undelivered		Rheumatic heart disease	No
Mrs. G	1950	Term	Low forceps	Postpartum hemorrhage, lower nephron nephrosis (transfusion)		Yes
Mrs. H	1950	20 weeks	Natural	Toxemia		Yes

DR. JOSEPH L. BAER.—It must be plain that the work being done in Milwaukee Hospital is on a very high plane of efficiency. The figures presented would not be obtainable if there were not the close supervision which the staff is in a position to exercise in that institution; and that in face of the fact that 30 per cent of the staff is in the general practitioner group. Obviously that kind of result can be obtained only where the staff is alert and efficient.

The maternal deaths in 1949 in 223 hospitals in Illinois numbered 113, i.e., 0.065 per cent. In Wisconsin it was 0.06 per cent, a highly creditable record.

For the last seven years there have been 16,000 deliveries at Michael Reese Hospital. Of that number, eight women died. That is a maternal mortality of 0.05 per cent. That is not an irreducible minimum by any means and still it is a figure considerably lower than average the country over.

The figures for the city of Chicago are obtainable monthly. This was started in 1930, at which time there were 58,000 deliveries with a death rate of 4.7 per 1,000. In 1949, there were 78,000 deliveries and the death rate was 0.07 per cent. If we take into consideration not the deaths but the survivals, we must realize how much progress has been made. Let us take the 1936 figure as the dividing line because during the years 1933 to 1936 a Committee of this Society studied the maternal mortality in the city of Chicago and came out with a number of recommendations and to a certain extent a constructive criticism of the situation in an enormous number of hospitals in this city. The Joint Maternal Welfare Committee of Cook County was established in 1937 under the auspicies of the Commissioner of Health. If we take the figures just before the operation of the Joint Maternal Welfare Committee, there were roughly 64,000 deliveries with 106 maternal deaths from all causes. If that were projected at that rate the maternal mortality through the next fourteen years would have been much higher and the number of deaths would have been 2,228. With the decrease in maternal mortality the number was 1,400 for the entire fourteen-year period after the establishment of the Joint Maternal Welfare Committee. During the fourteen years, assuming the number of births remained at 48,000, there would be 845 women whose lives were not lost in confinement. We think it is right to emphasize that as the obstetrical

measures and controls improve, the number of women who *survive* is appreciable. In 1949 there were 72,000 deliveries. Through the intervening years the number of births have gone up considerably and the number of survivals on a percentage basis has been that much greater.

I want to present a figure which again revolves around the work of the Joint Maternal Mortality Committee. There is a Subcommittee, the Committee on Maternal Mortality, which for these fourteen years has met faithfully once a month to analyze the causes of death of the women who died under the diagnosis of maternal death. That includes septic abortion as well as all pregnancy complications in the women who died. There were 60 maternal deaths in 1948. The percentage in 1948 was 0.7, the same as 1949. The Subcommittee analyzed these 60 deaths, and the approach for the analysis is the decision whether that death is to be classed as an obstetrical death or a nonobstetrical death. If it is to be classed as an obstetrical death, then the Committee attempts to determine whether there were preventable factors in the death of that woman. Very rarely does the Committee use the phrase "preventable." Almost always the phrase "preventable factors" is used. Finally the Committee attempts to assign responsibility.

Of the 60 women who died in 1948, there were 12 whose deaths were classified as nonobstetrical. These could be from auto accidents during pregnancy, etc. There were 48 obstetrical deaths. There were 17 classified as "preventable" or with "preventable factors." So among the 60 deaths we found 17 women who died and in whose case histories, including the therapy used or omitted, there was evidence that they might have been saved. That is a very definite indication that among obstetrical deaths at least one-third might have been prevented. Therefore, we are only on the way toward the irreducible minimum.

There were 15 cesarean sections among these 60 who expired in 1948. Of the 15 cesarean sections there were 8 low cervical cesarean sections, one with myomectomy, seven classical sections, three with hysterectomy following cesarean section, and one ruptured uterus in a woman who previously had had a section. I am trying to emphasize the fact that in spite of all our care, supervision, and attempts at control among innumerable hospitals in Chicago, nevertheless there were 15 deaths following cesarean section—25 per cent of the total. Of those 15, seven were of the classical type.

DR. CHARLES NEWBERGER.—Undoubtedly you are familiar with the current program in downstate Illinois. Dr. Baer told you what the Joint Maternal Welfare Committee is doing in the city of Chicago. Illinois, outside the city of Chicago, has a similar study under the auspices of the State Health Department and the State Medical Society. In 1948, in 103,777 live births the maternal death rate was 0.87 per 1,000 live births. In 1949, in 107,015 live births the rate dropped to 0.75, and this year with two weeks to go it is 0.73.

Out of 224 deaths classified as maternal during this period of three years, 36.6 per cent were due to hemorrhage, 26.8 per cent were due to toxemia, and sepsis was responsible in 12.0 per cent; the remaining 24.6 per cent were due to various causes. These figures are presented by way of contrast with the experience at the Milwaukee hospital.

DR. EUGENE A. EDWARDS.—I would like to say a word in favor of early ambulation. Dr. Hofmeister reported on three women who died of thrombophlebitis. Since we started early ambulation—and when I say early, I mean getting the patient out of bed the first night and every morning and night thereafter—we have had absolutely no thrombophlebitis in our hospital. I cannot help but defend early ambulation. I think three deaths from thrombophlebitis should make us feel that the more we get these patients out of bed the first night, the first day, and the second day, the less thrombophlebitis we will have.

DR. HOFMEISTER (Closing).—We have had two deaths from embolism but none since early ambulation was instituted in 1939. I want to re-emphasize that only by careful prenatal care and adequate and sound judgment in the conduct of labor, together with thorough maternal education during the prenatal period, which must be preceded by intelligent premarital examinations and advice, will we be able to reduce still further the "irreducible" minimum in maternal mortality.

Department of Case Reports New Instruments, Etc.

MALIGNANT THECOMA OF THE OVARY

FRANCIS E. PROCTOR, M.D., F.A.C.S., JOSEPH P. GREELEY, M.D., AND THOMAS K. RATHMELL, M.D., TRENTON, N. J.

(From the Departments of Gynecology and Pathology, Mercer Hospital)

THECOMAS, the origin of which has been the subject of much speculation,[1] are generally regarded as self-limiting ovarian tumors. Since their separation as a clinical entity in 1932 by Loeffler and Priesel,[6] a total of approximately 82 cases has been reported,[7] of which only four have been classified as malignant.[3, 4, 5, 6] The death of this patient, due to this generally benign tumor, led to a survey of the literature in an effort to define more clearly the clinical and surgical aspects of "metastasizing thecomas" as contrasted with those which remain self-limited; at the same time, the histopathologic features of the surgical and autopsy specimens are presented.

Case Report

Presentation of a Case.—D. T., a 52-year-old Russian-born woman, was first seen in the outpatient department because of vague suprapubic pain and constipation. Interpretation of her complaints was difficult because of the language factor. Physical examination at that time showed a granular cystic cervix, a uterus enlarged one and one-half times, with palpable nodules in the subserosa which were regarded as fibroids. At the time she was first seen, routine studies showed a hypochromic anemia, an absence of free gastric hydrochloric acid, and radiographically normal gastrointestinal and biliary tracts. An intravenous pyelogram and urinalysis were not remarkable. The patient's obstetrical history revealed that she was gravida iv, para ii, one miscarriage having occurred at 2½ months and the other at an unknown period of gestation. Catamenia was at 15 years of age, with a 28-day periodicity and a duration of five days. Recently the periods became irregular, occurring every 2 to 3 months with slight bleeding. No menopausal symptoms were present.

The patient refused permission for operation and did not return to the clinic for six months. At this time she complained of severe pain on defecation. The abdomen was swollen, tense, and painful to palpation. The mucous membranes of the vaginal tract were pale and the uterine fundus and posterior cul-de-sac were "fixed." Nodular masses were palpated in the cul-de-sac. A diagnosis of carcinoma was made and laparotomy was recommended. Permission was granted.

At operation, 2,500 c.c. of turbid gray fluid were aspirated from the peritoneal cavity. The whole peritoneal surface was thickened and covered with small papillary gray-white plaques. These were soft and from 1 to 3 mm. in diameter. Gross visualization of the peritoneum suggested a tuberculous peritonitis except that the plaques were larger than one usually sees, and appeared granular and noncaseous. Both ovaries were enlarged, of similar appearance, irregularly nodular, with rugaelike folds purple in color, and situated beneath the uterus, to which they were adherent through easily separated fibrous adhesions. The tubes were bluish in color.

The intestines presented an unusual picture. They were not involved in the pelvic adhesions. The entire intestinal tract was small and collapsed. The mesentery was thickened to such a degree that it brought the ileum into a cluster which could be covered by the hand. There was an apparent mass in the base of the mesentery but this could not be identified with certainty because of the thickened peritoneum. The gall bladder was normal in appearance. The greater curvature of the stomach seemed free but the organ appeared contracted. The omentum was about 1 cm. in thickness and hard. A portion was removed with both tubes and ovaries for biopsy.

Postoperatively, a diagnosis of bilateral ovarian cysts with tuberculous peritonitis was suggested.

Surgical Pathology.—Examination of the formalin-fixed tissues removed at laparotomy showed the mesenteric biopsy to measure 2 by 1 by 1 cm., with a yellow-colored surface which on section showed an areolar stroma with broad bands of interlacing pink-white fibrous strands.

One tube measured 5 by 1.1 cm., the other 4.7 by 1 cm. Both were bluish-white in color, thickened, and moderately firm in consistency. Several white, circumscribed, raised nodules 1 to 2 mm. in diameter were noted on the serosal surface and within the wall of the tubes.

One ovary was intact, measured 5.5 by 4.5 by 3.5 cm. It showed a tan, nodular surface, with areas of firm, white fibrous tissue interspersed. When sectioned, the capsule was thickened to 0.5 cm. in area. One pole was markedly edematous. Throughout the gray-white stroma, small nodules similar to those seen on the tubes were visualized. A follicular cyst was present.

The opposite ovary measured 6.8 by 5.5 by 3 cm. Its stroma appeared similar to the opposite ovary, and supported a cyst 1.2 cm. in diameter containing blood-tinged fluid.

Microscopic study of the surgical specimen showed marked structural alterations in the ovarian stromal pattern (Figs. 1, 2, and 3) consisting of interlacing bundles of spindle cells displaying vesicular nuclei, prominent eosinophilic nucleoli, and, in areas irregularly distributed throughout the stroma, masses of hyperchromatic cells with 4 to 5 nuclei in a cluster, giving one the false impression of giant-cell formation. A similar histological pattern was present in the section of the opposite ovary which contained a corpus luteum with hemorrhage.

Section of the mesentery showed invasion by tumor cells, as did sections of the tubes. The tumor cells were most conspicuous adjacent to the mesosalpinx.

Surgical convalescence was not favorable. The patient complained of continued pain in the abdomen, ascites recurred and was relieved by paracentesis, at which time 6 L. of turbid fluid were again removed from the peritoneum. Cultures of the ascitic fluid, after concentration, were negative for acid-fast bacilli. The patient died ten weeks after laparotomy.

Postmortem Study.—At autopsy the significant findings were an incompletely healed midline scar of the abdomen; the entire gastrointestinal tract below the esophagus was incapable of being dissected into its component parts. It formed a solid mass covered by a white neoplastic tissue of almost cartilaginous consistency which destroyed all lines of cleavage. The stomach, intestine, colon, genitourinary organs, pancreas, and left adrenal gland were removed en masse and hemisectioned (Fig. 4). The retroperitoneal space was free of any neoplastic tissue and dissected readily. The prevesical space of Retzius was uninvolved. On cross section, the stomach wall was thickened, the mucosa hemorrhagic, and the lumen narrow. The omentum was diffusely invaded by white neoplastic tissue and was contracted into the area between the stomach and transverse colon. The mesentery of the small bowel was likewise diffusely invaded and contracted. The serosal surfaces of the intestine were thickened and blended with one another through dense fibrous adhesions. The lumen of the small bowel was contracted, and contained green-stained mucus; its mucosa appeared normal. The left ureter was indistinguishable in a mass of neoplastic tissue at the pelvic brim.

The cervix was inflamed about the external os. The uterine musculature appeared normal. The endometrium was atrophic. The reflections of the peritoneum over the bladder, uterus, and posterior cul-de-sac showed discrete and confluent plaques of neoplastic white tissue.

Fig. 1.

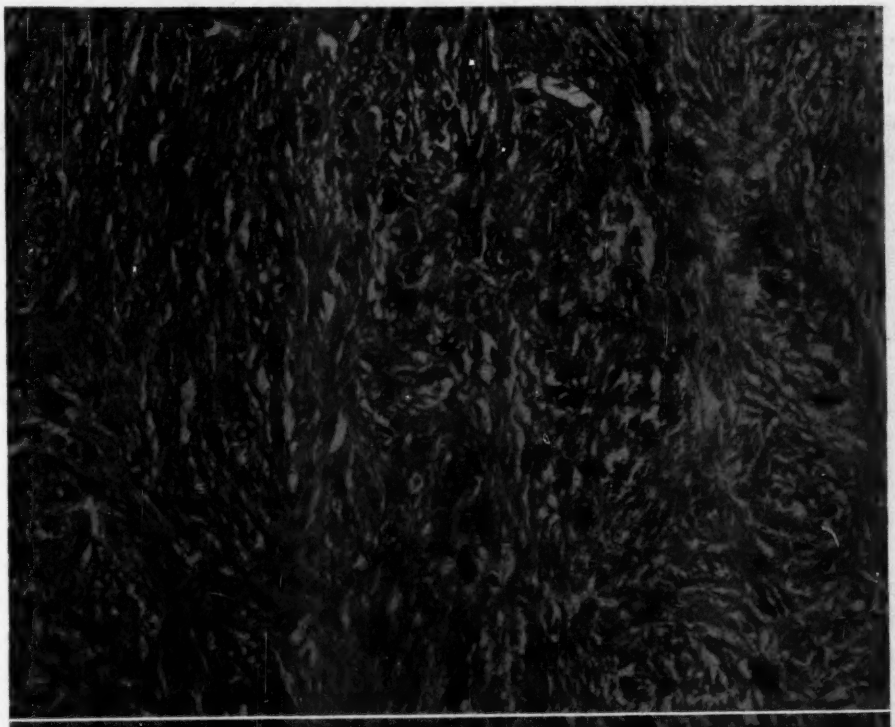


Fig. 2.

Fig. 1.—Photomicrograph of ovarian tumor illustrating irregular interlacing pattern of broad epithelioid spindle cells. (×175.)

Fig. 2.—Another area of tumor showing contrasting pattern of multinucleated thecoma cells. (×175.)

The microscopic appearance of both ovaries and the diffuse peritoneal metastasis was one which suggested a sarcomatous pattern. Postmortem histological studies showed metastatic tumor invasion of all muscle coats and submucosa of the stomach and intestine (Figs. 5 and 6) with metastatic extension to the peripancreatic tissue (Fig. 7) and myometrium. The involved tissues removed at autopsy shows a histological pattern similar to the surgically removed tubes and ovaries.

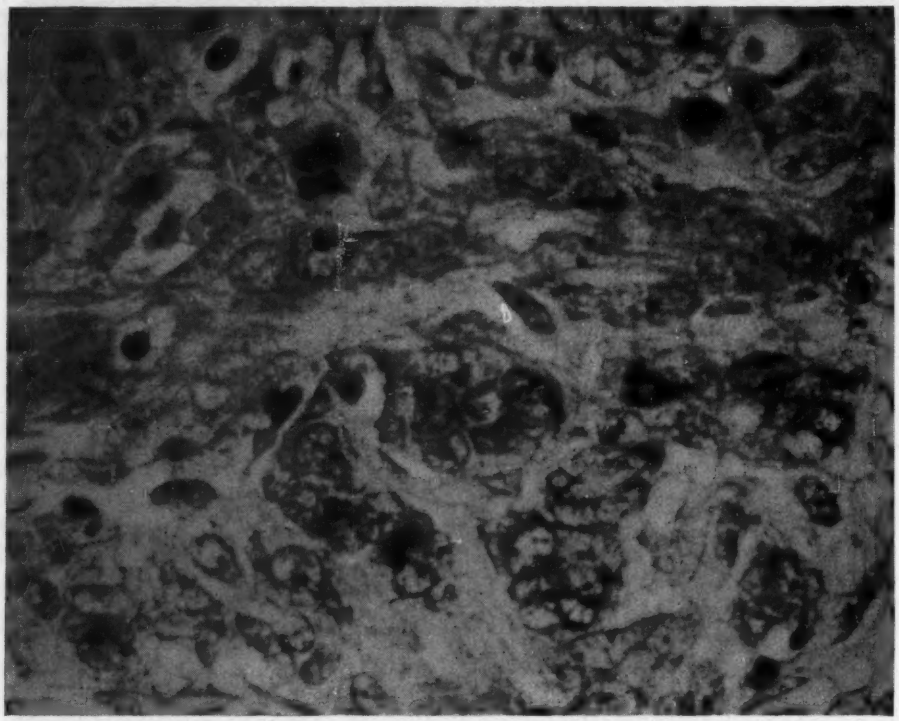


Fig. 3.—Photomicrograph of tumor showing multinucleated cells, frequent mitoses and vesicular nuclear pattern with prominent nucleoli. (×400.)

Geist and Gaines[3] and Wolfe and Neigus[10] have demonstrated the presence of fat in these tumors and have correlated the endocrine potentialities in a roughly quantitative manner with the presence of lipid material. We were able to demonstrate a positive reaction for fats by sudan IV staining of the formalin-fixed metastases secured at autopsy from the serosal surface of the uterine fundus.

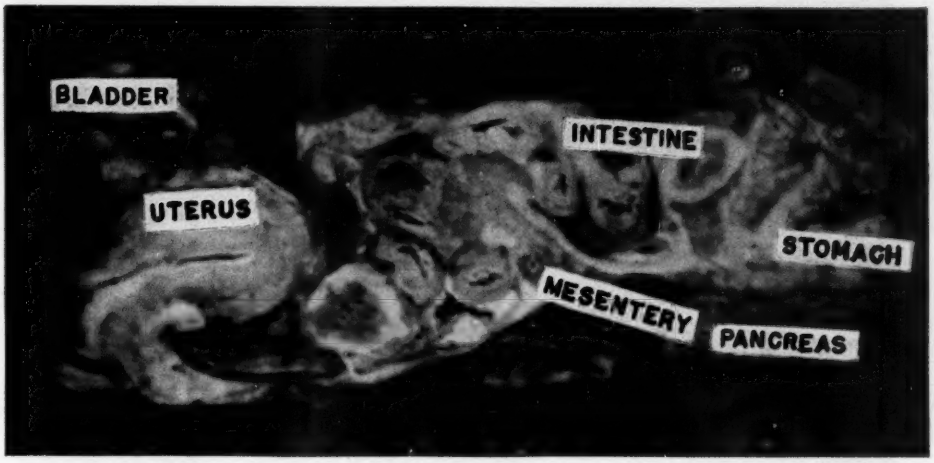
The Liebermann-Burchard reaction has been used to demonstrate the presence of steroid components in hormone-producing ovarian neoplasms.[8] Reddish-brown particles are indicative of a positive reaction, and these were repeatedly demonstrated in our material (Fig. 8) in the areas which by hematoxylin and eosin stain showed the presence of tumor.

Our material was submitted to Dr. Emil Novak for inclusion in the Registry of Ovarian Tumors. He stated, "I am inclined to agree with you that the tumor represents a thecoma of malignant type with the metastases above described."[9]

Comment

A clinical diagnosis of theca-cell tumor when limited to the ovary is difficult to make, if not impossible, with our present methods of examination. When the tumor assumes malignant characteristics, however, the diagnostic criteria are the same as for any metastasizing intraperitoneal tumor, a variably palpable mass with ascites and genitourinary-gastrointestinal complaints. We

Fig. 4.



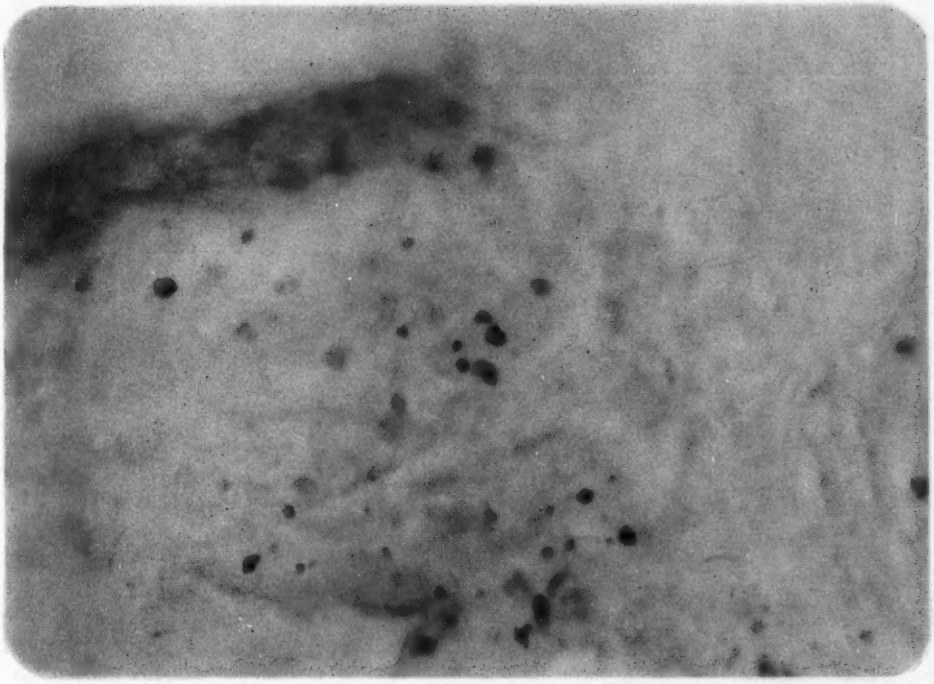


Fig. 8.

Fig. 4.—Hemisection of abdominal viscera. Note plateaulike cluster of intestine about mesentery and uninvolved retroperitoneal tissues, result of metastasizing the coma.

Fig. 8.—Photomicrograph demonstrating steroid materials having a reddish-brown appearance by the Liebermann-Burchard reaction, from metastatic tumor tissue on the serosal surface of the uterine fundus. (×800.)

Fig. 5.

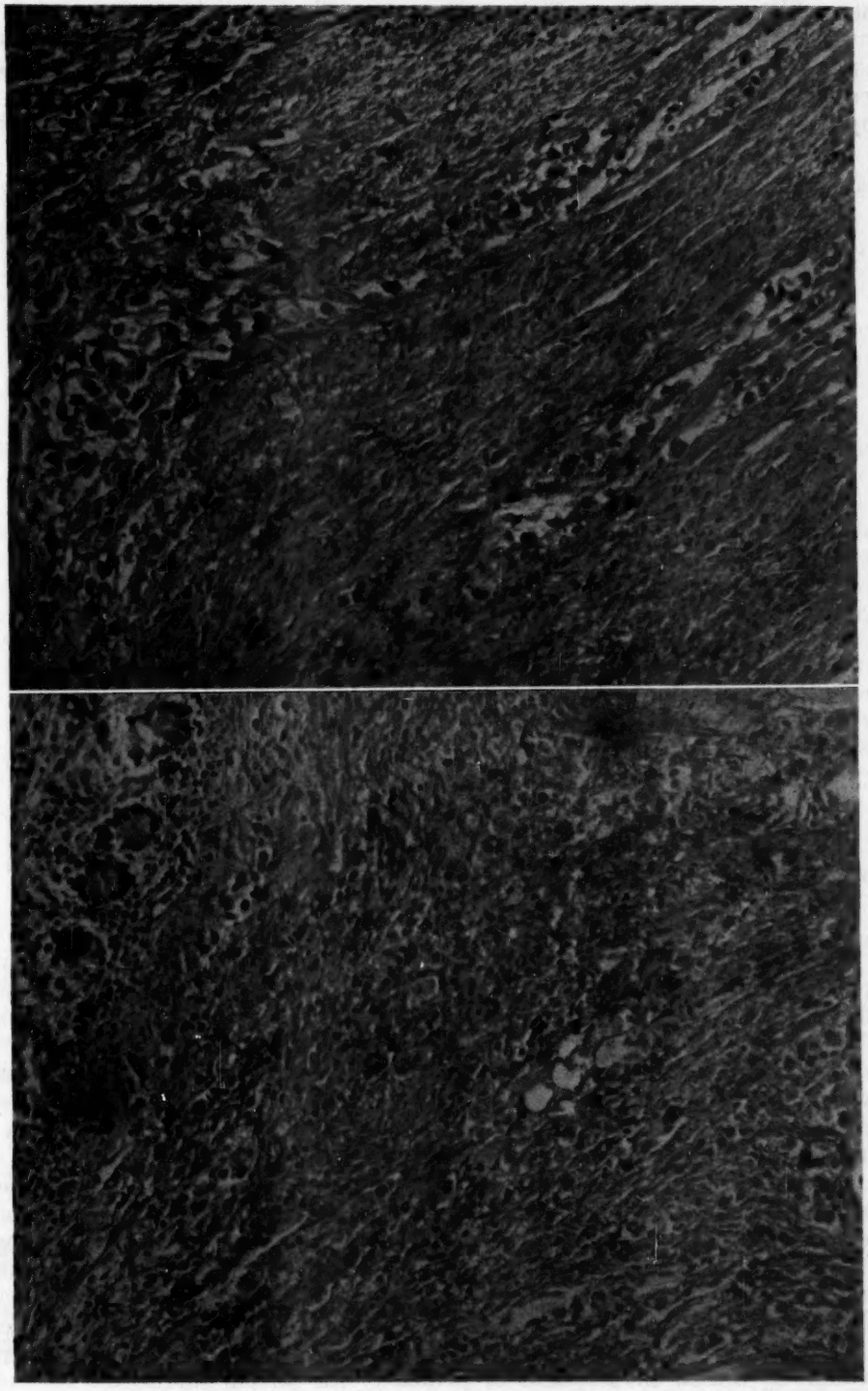


Fig. 6.

Fig. 5.—Photomicrograph showing tumor cells invading intestinal musculature. (×130.)
Fig. 6.—Similar invasion of the submucosal tissues of the intestine. (×130.)

feel that the latter occur early because of the desmoplastic potentialities of the tumor which, everywhere, presents a predominantly sarcomatous pattern and has been frequently misdiagnosed as a fibrosarcoma. The menopausal age of the patient and the demonstration of an endometrial estrogenic effect (unopposed *after* the menopause) in the presence of the previously mentioned signs and symptoms can limit the differential diagnoses to granulosa-cell tumor and theca-cell tumor.

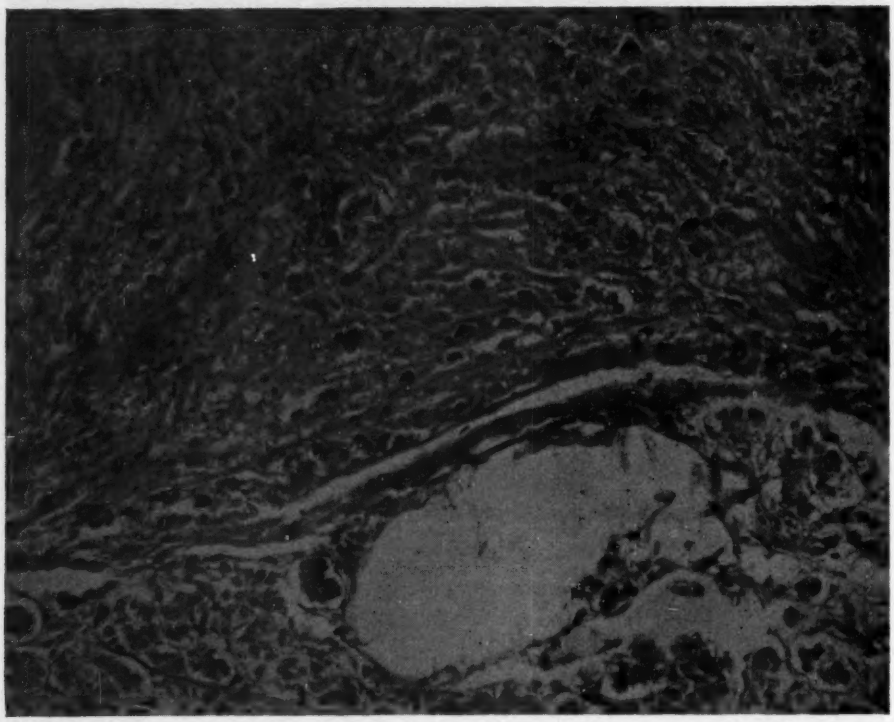


Fig. 7.—Illustrating peripancreatic extension of the tumor tissue. (×130.)

The most prominent symptom of this tumor in postmenopausal patients is atypical bleeding.[3] The bleeding may be cyclic or irregular, profuse or scanty. There may also be noted a rejuvenation of breast tissue, recrudescence of libido, and a revitalization of the vaginal mucosa.[7] The uterus may enlarge. The endometrium presents a hyperplastic picture resembling that in other conditions presumed due to hyperestrinemia.[3] Ascites has been noted in the clinical history of all metastasizing thecomas. Occasionally an ovarian fibroma with ascites and hydrothorax (Meigs' syndrome) may be confusing clinically.

At operation the abdominal picture may simulate a tuberculous peritonitis as presented. All previous cases have been unilateral, but our case, in its advanced state, was bilateral, presenting a similar gross appearance to the surgeon and with histological sections of the individual ovaries displaying tumor tissue within the ovarian parenchyma rather than on the surface of one ovary as might be expected if it were metastatic by implantation. That implantation is the method of spread rather than by way of the lymphatics or the blood stream is evident by diffuse involvement of primarily the serosal surfaces.

The lipid and steroid content of these tumors which in this case was also demonstrated in its metastases provides a histochemical segregation of the tumor from ovarian fibromas and sarcomas.

Histogenesis of this tumor has been controversial. Faulconer and Butcher regard it as a derived tumor. They state that: "Theca cell tumors differentiate from the ovarian stroma under the stimulus of the granulosa elements adjacent to that tissue." Their concept is shown in Table I.

TABLE I. HISTOGENESIS OF ENDOCRINE TUMORS[2]

ADULT OVARY	GENITAL PRIMORDIUM	ENDOCRINE TUMORS
Granulosa cells, rete ovarii	Sex cords	Granulosa cell tumor, arrhenoblastoma
Ovarian stroma, theca cells	Mesenchyme	Thecoma, arrhenoblastoma, hilus-cell tumor, adrenal-like tumor
Ovum	Primitive germ cell (by migration)	

While the previous studies of this tumor have been based on observations of surgical materials, we have presented the relevant findings and studies from both surgical and autopsy materials. We expect to create thereby a greater familiarity of the profession with the malignant potentialities of this tumor and to aid in its establishment as a separate diagnostic entity.

The pathologist who visits the surgical amphitheater may be alerted to the diagnosis of malignant thecoma by the surgeon's statement that he is able to gather the clustered small bowel into the confines of his cupped hands from a plateaulike base. This impression may be further substantiated if gray-white granular implants 2 to 3 mm. in diameter can be recognized on the serosal surface of the bowel or about the peritoneum.

The four cases of malignant thecoma which have been recorded in the literature constitute sufficient justification for panhysterectomy whenever the lesion is suspected in women in or beyond the menopausal age. These tumors may be reduced in size but not destroyed by radiation therapy.[7] Therapeutic measures, when instituted early in the study of the patient with pelvic tumor of this type, may prove lifesaving.

Summary and Conclusions

1. Clinical features, surgical pathology, and postmortem studies from a case of bilateral metastasizing thecoma of the ovary are reported.

2. Metastasizing thecoma must be considered in the differential diagnosis of all malignant tumors in the menopausal patient.

3. Metastasis of this tumor appears to be by contiguity of adjacent serosal surfaces, with the constant production of ascites and obstructive phenomena of the genitourinary or gastrointestinal tract.

4. The preferred therapy in these cases is early surgery.

The authors wish to acknowledge the courteous review of the histological materials from this case by Dr. R. Philip Custer of Philadephia and Dr. Emil Novak of Baltimore.

References

1. Dockerty, Malcom B.: AM. J. OBST. & GYNEC. 39: 434, 1940.
2. Faulconer, R. J., and Butcher, J.: Proc. Path. Soc. Philadelphia, pp. 38-93, Nov., 1949-May, 1950.
3. Geist, Samuel H., and Gaines, Joseph A.: AM. J. OBST. & GYNEC. 35: 39, 1938.
4. Huber, H.: Zentralbl. f. Gynäk. 61: 14, 1937.
5. Loeffler, E., and Priesel, A.: Wien. med. Wchnschr. 84: 400, 1934.
6. Loeffler, E., and Priesel, A.: Beitr. z. path. Anat. u.z. allg. Path. 90: 199, 1932.
7. McGoldrick, Joseph L., and Lapp, Warren A.: AM. J. OBST. & GYNEC. 48: 409, 1944.
8. McKay, D. G., Robinson, D., and Hertig, A. T.: AM. J. OBST. & GYNEC. 58: 625, 1949.
9. Novak, Emil: Personal communication.
10. Wolfe, Samuel A., and Neigus, Irwin: AM. J. OBST. & GYNEC. 42: 218, 1941.

CONCERNING PREGNANCY AFTER URETEROINTESTINAL ANASTOMOSIS

FRANK HINMAN, JR., M.D., SAN FRANCISCO, CALIF.

(From the Department of Urology, University of California School of Medicine)

THE application of the newer techniques of anastomosis[2, 4, 5, 7] and the use of effective antibiotic therapy permit more patients to live longer and in better health after ureterointestinal transplantation. Consequently, the question of permitting female patients after anastomosis to bear children is more often raised. In recent years, we as urologists have been called on with increasing frequency to decide the necessity of sterilization in these patients.

As early as 1927, Peterson[9] said, "What will happen to women who have had the ureters transplanted in case of pregnancy? Although not reported I am given to understand that one of Charles Mayo's cases went to full term after this operation and was delivered safely of twins. Evidently the dangers of pregnancy will depend upon how much if any renal infection may be present as a result of this operation. Obviously it would be unfair to these women to sterilize them for possible dangers which may never exist." However, little subsequent expression of opinion can be found. A recent review of the literature[10] showed that 26 women with exstrophy of the bladder, a few of whom in addition had transplanted ureters, gave birth to 33 children.

Three possible contraindications exist for pregnancy in the presence of exstrophy with ureteral transplants. One is the possibility of transmission of the defect. However, little statistical evidence can be found for such inheritance.

A second objection is the possibility of damage to the genital tract. Three nulliparous women are reported with genital prolapse.[1, 3, 6] We have recently seen a fourth patient in whom operative fixation was performed in order to allow for pregnancy.[8] Six of the 33 deliveries reported, not including one of our own, were by cesarean section either to avoid prolapse or because of disproportion. In addition, cesarean section, especially if repeated, might further weaken the congenitally inadequate anterior abdominal wall. However, in partial refutation of these theoretical objections are the reports of 19 vaginal deliveries and 6 sections without untoward difficulties. The fact of 8 stillbirths among these 33 births should not absolutely contraindicate pregnancy in these women.

The third objection, the one which concerns us most as urologists, is the possibility of renal damage. This can be brought about by pressure of the fetus on the ureters or by hormonal action on ureteral tone. This is not the place for a discussion of the relative actions of these factors, for the net result would be the same: obstruction, stasis, and infection.

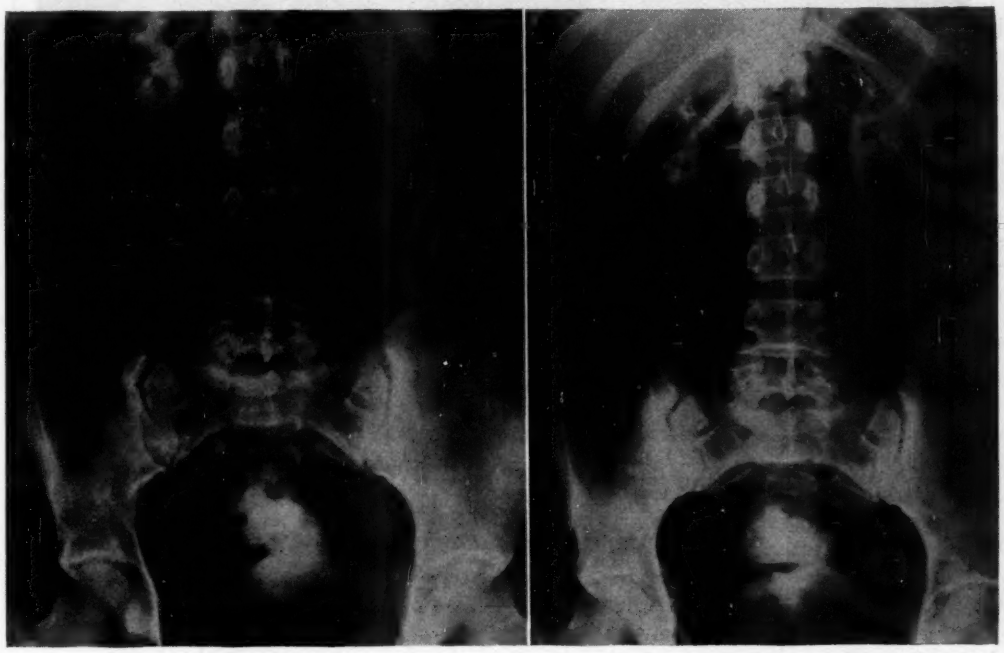
Since most anastomoses, for technical reasons, are made at or just below the brim of the pelvis, compression of the ureters by the enlarging uterus will probably be as great as in the normal individual. Physiologic dilation of hormonal etiology would be expected to be no greater than in patients without transplantation. The effects of compression and hormones would be expected to be more damaging to the transplanted ureter since it is now believed that unobstructed peristalsis and urine flow, rather than valve action, are the principal protections against the establishment of renal infection.

For data regarding these effects we must fall back on our own clinical experience.

Material

Fifty-five female patients have been subjected to uretero-enterostomy on the University service in the 30 years since 1919. Fourteen of these women were operated upon for exstrophy. Of these 14, 6 were operated upon too recently to have yet reached the age for marriage. Two died postoperatively. Of the remaining 7, 2 have had children and their cases are reported below.

The remaining 41 patients with ureteroenterostomy were operated upon because of irreparable vesicovaginal fistula or incontinence, intractable vesical tuberculosis, or (with cystectomy) for carcinoma. There were only 3 of this group who were under 40 years of age, married, and who survived the operation for a sufficiently long period to conceive. No pregnancies have occurred in these 3 patients, but 2 have been followed too short a time.



a. b.

Fig. 1.—Patient L. P., ureteral transplantation, 1919. a, Intravenous urogram, 1939. b, Same 1947, 5 years after pregnancy.

CASE 1.—The first patient to conceive was a girl who was 5 years of age when her left ureter was transplanted by a modified Coffey I procedure in 1919 for vesical exstrophy. The following year, the right ureter was similarly transplanted and 4 years later the bladder was excised. In 1942, at the age of 28 years, she underwent cesarean section with delivery of a normal boy. Because her obstetrician felt another section was inadvisable, she was sterilized at that time. She suffered from no renal difficulties during the pregnancy, and subsequent followup has demonstrated no harmful effects on renal function and no flare-up of infection. Intravenous urograms made before and after pregnancy reveal no significant change (Fig. 1).

CASE 2.—The second patient was 18 years of age in 1940 when right ureterointestinal transplantation, followed in two weeks by left anastomosis, was done for vesical exstrophy. Following operation, she had bouts of pyelonephritis every 3 to 4 months. Four years after transplantation, she became pregnant but aborted spontaneously at 4 months. Eight years after operation, she was delivered vaginally of a normal female child. Her recent spontaneous comment was that the pregnancy greatly helped her kidneys, for she has had no

bouts of pyelonephritis since the time of conception. Urograms made during the seventh month of pregnancy revealed no increased dilation compared with previous films (Fig. 2).

Although the example of two patients cannot be used to prove the harmlessness of pregnancy after anastomosis, it does suggest that, at least in some individuals, childbearing can be tolerated.

Fig. 2.—Patient A. R., ureteral transplantation, 1940. a, Intravenous urogram 1941. b, Same, 1948, after 7 months' pregnancy.

Summary and Conclusion

1. Ureterointestinal anastomosis is now performed more frequently and more successfully. Women with such transplants can be expected to lead happy married lives. Sterilization or hysterectomy, which were customary in the past, limits the complete fulfillment of marriage.

2. Although it might be assumed that the physiologic dilation or obstruction to the upper urinary tract during pregnancy would be harmful to the individual, actual evidence supporting such an assumption has not been forthcoming.

3. On the contrary, two patients at the University Hospital have borne two children without evident damage. One woman experienced actual clinical improvement during and following pregnancy.

4. We would conclude that unless very marked renal obstruction and infection exist with seriously diminished renal function, women with ureterointestinal transplants should be allowed to bear children.

References

1. Clayton, S. G.: J. Obst. & Gynaec. Brit. Emp. 52: 177, 1945.
2. Cordonnier, J. J.: Surg., Gynec. & Obst. 88: 441, 1949.
3. Damm, P. N.: Zentralbl. f. Gynäk. 61: 440, 1937.
4. Hinman, F., Jr., and Hinman, F.: J. Urol. 64: 457, 1950.
5. Hinman, F., Jr.: J. Urol. 64: 567, 1950.
6. Ismail, M.: J. Egyptian M. A. 22: 587, 1939
7. Nesbit, Reed M.: J. Urol. 61: 728, 1949.
8. Overstreet, E.: To be published.
9. Peterson, R.: Trans Am. Gynec. Soc. 52: 5, 1927.
10. Rubovits, F. E., and Arnkoff, M.: J. Urol. 62: 52, 1949.

CONGENITAL ECTOPIC OVARY

DAVID H. NICHOLS, M.D., AND ANTHONY V. POSTOLOFF, M.D., BUFFALO, N. Y.

(From the Millard Fillmore Hospital)

CONGENITAL absence of one or both ovaries is a rare condition, and only two such reports have been found.[1, 2] Apparently no one has described a case similar to the one which was recently brought to our attention. The findings were those of a congenital absence of the right kidney, ureter, and Fallopian tube, with an ectopic displacement of the right ovary.

Case Report

Mrs. G. S., aged 36 years, was admitted to the hospital on April 25, 1950, because of sharp, stabbing pain in the right upper and lower quadrants with urinary frequency, burning, and nocturia. There had been a similar episode which passed quickly without treatment one year ago. Past history revealed only an appendectomy eleven years previously and no other illness. There had been one normal full-term pregnancy seventeen years previously, but no abortions or miscarriages. The family history was negative for congenital abnormalities. Menses began at age 13, recurred regularly every twenty-eight days, and the duration of flow was approximately four days. The last menstrual period began April 29, 1950, and lasted for three days. The previous menstrual period was from April 1, 1950, to April 4.

Physical examination on admission revealed a well-developed, obese, white woman. The breasts and external genitals were normal. The abdomen was rounded, and there was tenderness without spasm in the right upper and lower quadrants. A mass approximately 5 cm. in diameter was palpated anteriorly midway between the umbilicus and the right iliac crest.

Cystoscopic examination by Dr. George Slotkin showed absence of a right ureteral orifice. Intravenous Diodrast pyelograms revealed hypertrophy of the left kidney, but no shadows or visualization of the right kidney or ureter. Cholecystography demonstrated cholelithiasis.

On May 2, 1950, the abdomen was opened (Fig. 1, A) by Dr. Henry Kenwell, whose operative note read as follows: "On opening the peritoneal cavity no free fluid was found. Retroperitoneal examination of the right side from the diaphragm to the pelvis confirmed the absence of the right kidney and ureter. Underneath the liver, at the level of the gallbladder, a mass of cystic tissue measuring 10 by 5 by 3 cm. was found. This was attached by a broad pedicle to the posterior peritoneum in the approximate position normally occupied by the right kidney (Fig. 1, B and C). This mass was resected. Examination of the pelvis revealed the left tube, broad ligament, and ovary to be grossly normal. The uterus was normal in size and position, but there was no evidence of any right tube or ovary in the pelvis. The right side of the uterus was perfectly smooth and clean (Fig. 1, D).

"The gallbladder was thickened and numerous concretions were palpated. A subserous cholecystectomy was done without difficulty."

The cystic mass was described as a serosa-covered portion of tissue 10 by 5 by 3 cm. which contained numerous cystic areas, the largest measuring 2 cm. in diameter. This cyst was lined by a yellow undulating membrane and contained a friable, gelatinous, blood-tinged substance (Fig. 2). Microscopic section of this tissue disclosed typical ovarian stroma with scattered follicle cysts and a hemorrhagic lutein cyst (Fig. 3). The clinical impression of chronic cholecystic disease was confirmed pathologically.

Embryologically, this case probably represents a disturbance in development of the mesonephros, with failure of growth of the right pronephric (Wolffian) duct. Absence of

this results in failure of development of the Müllerian duct. The genital ridge, however, developed sufficiently to form an ovary. (In early development the cephalic edge of the genital ridge extends far forward to the region of the liver.) • Absence of the caudal end of the mesonephros resulted both in failure of descent of the ovary, leaving it in its approximate embryonic position, and in absence of the right metanephric duct and tubules, causing failure of formation of the right kidney and ureter.[3]

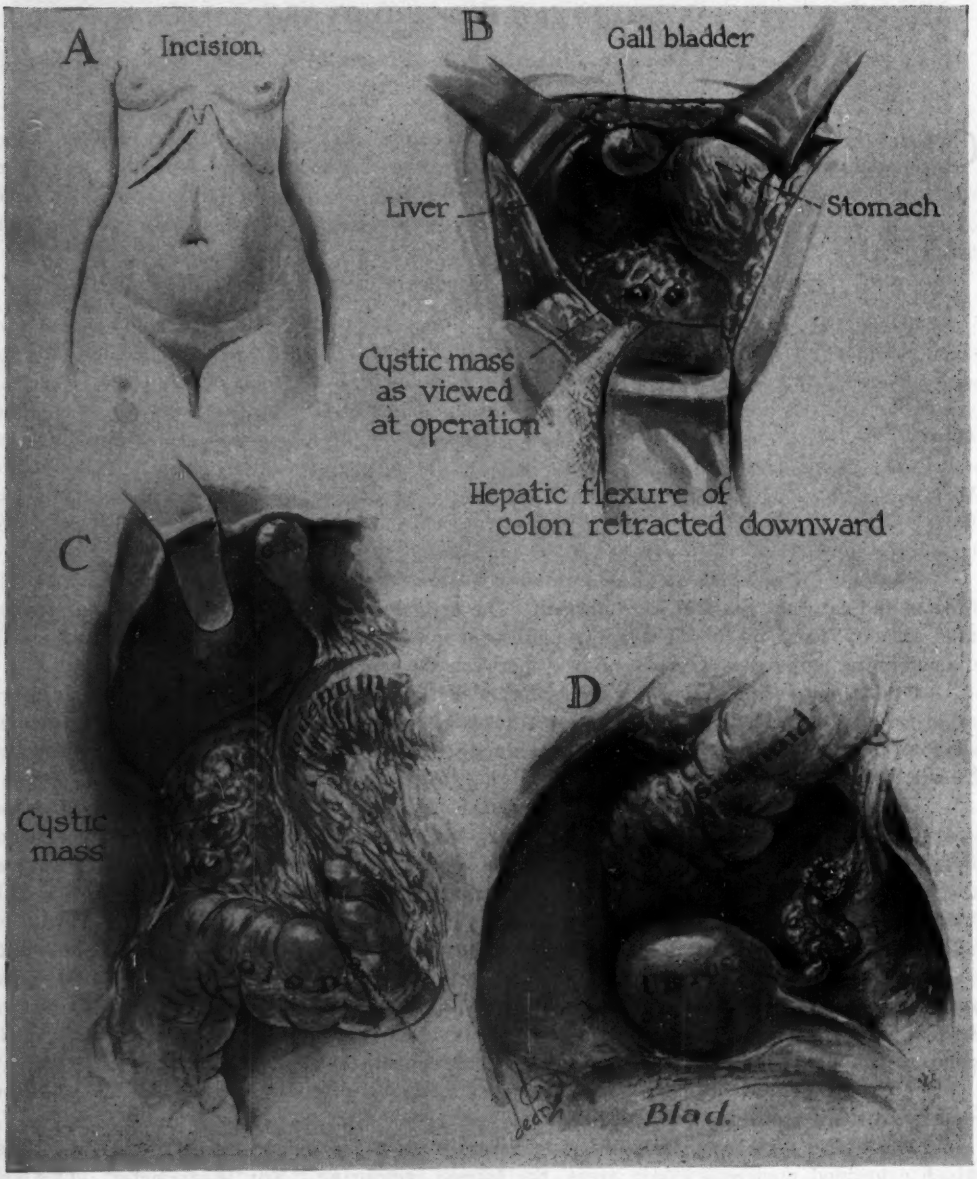


Fig. 1.—The pathology observed at surgery:
A. Location of the incision.
B. Cystic mass as viewed through incision.
C. Showing typography of cystic mass.
D. View of the pelvis from above showing absent right broad ligament, tube, and ovary.

Summary

A case of congenital absence of the right kidney, ureter, round ligament, and tube with ectopic (subhepatic) location of the right ovary has been presented, with its embryologic consideration. It is suggested that in any individual having apparent congenital absence of an ovary, careful examination of the posterior peritoneum from the diaphragm to the pelvis be performed to rule out an ectopic displacement of such a structure.

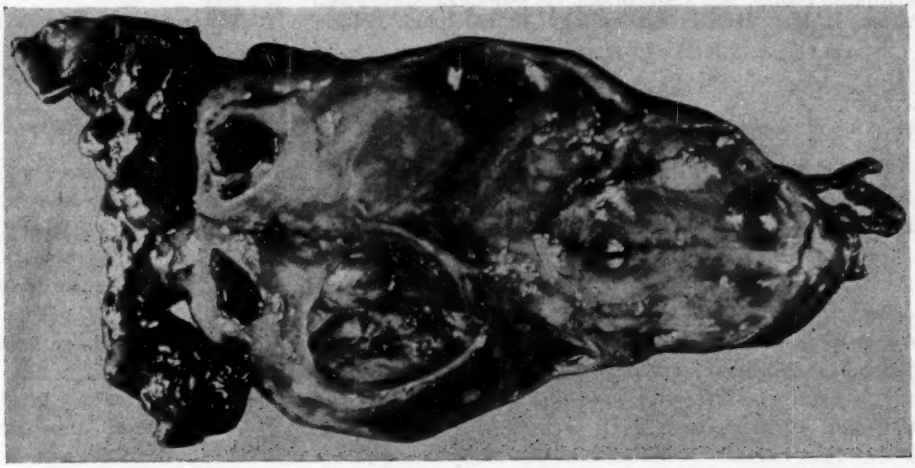


Fig. 2.—Cystic mass opened, showing large corpus luteum and smaller cysts.

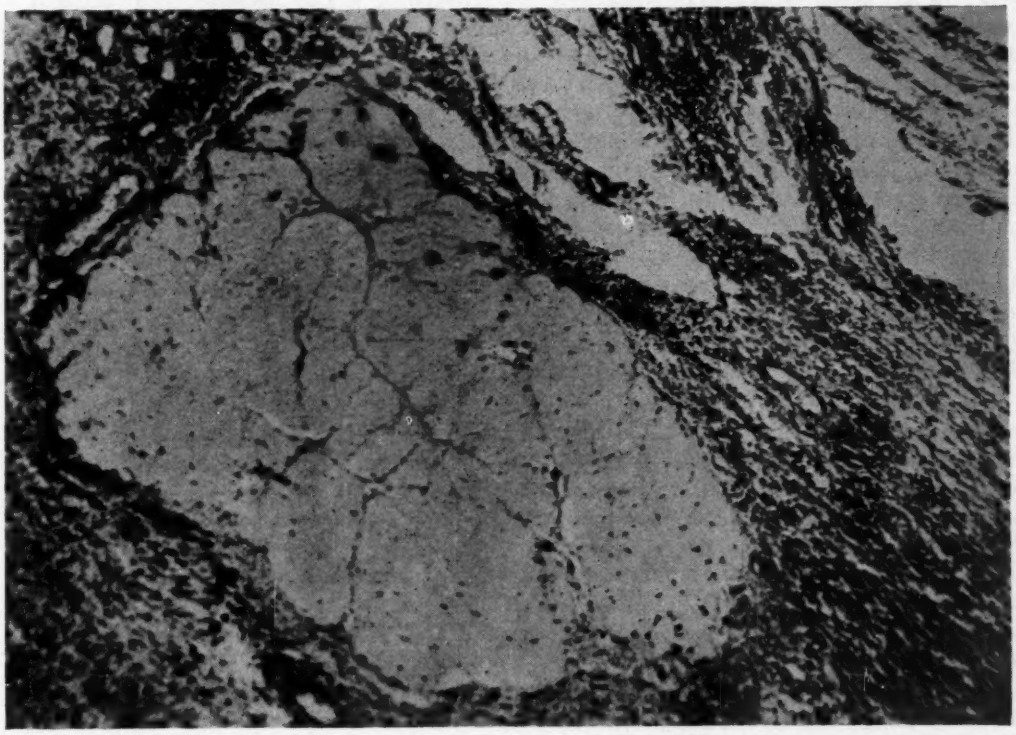


Fig. 3.—Photomicrograph of portion of mass showing ovarian stroma and a corpus albicans cyst.

The authors wish to express gratitude to Dr. Rufus Humphrey, Professor of Anatomy, University of Buffalo School of Medicine, for his valuable assistance in the preparation of the embryologic considerations of this paper, and to Mr. M. Dedrick, medical artist of the University of Buffalo School of Medicine for his excellent drawings.

References

1. Bjorkenheim, E. A.: Zentralbl. f. Gynäk. 59: 794, 1935.
2. de Aquino Salles, A.: An. brasil. de ginec. 13: 291, 1942.
3. Patten, B. M.: Human Embryology, Philadelphia, 1946, The Blakiston Company, p. 551.

HYPERPLASTIC CORPUS LUTEUM OF PREGNANCY, ASSOCIATED WITH CARCINOMA OF THE BREAST

JULES B. AARON, M.D., JACOB S. BEILLY, M.D., F.A.C.S., AND
NATHAN MITCHELL, M.D., BROOKLYN, N. Y.

(From the Departments of Obstetrics and Gynecology and Pathology of the Beth El Hospital)

IN a recent study of the human corpus luteum of pregnancy by Gillman and Stein,[1] the gross anatomical and histological features of corpora lutea of pregnancy were described. In all, thirteen specimens were examined. The size of the corpus luteum, the volume of the central cyst, and the thickness of the granulosa layer were quantitatively analyzed, with a qualitative and histochemical study of the lutein cells.

For the first fifty days of pregnancy there is scarcely any growth in volume or in diameter of the corpus luteum. At this age, the corpus luteum of pregnancy is equivalent to the size of a mature corpus luteum of menstruation and may measure as much as 1.8 by 1.2 cm. Between the fiftieth and sixtieth days the corpus luteum doubles its premenstrual area and may measure up to 2.0 by 2.5 cm. This enlargement is due primarily to increased formation of fluid in the central cavity and increased thickness of the fibrous tissue lining the wall of this cavity. As much as 1.75 c.c. of fluid were contained in the central cavity of one of the specimens. The lutein wall averages 5 mm. in thickness and remains fairly constant in size throughout the pregnancy. The fibrous tissue rim averages 1.5 mm. Approximately 25 per cent of the enlargement is due to hyperplasia and hypertrophy of the granulosa lutein and theca lutein cells. By the eightieth day, it is again reduced to the size of the premenstrual corpus luteum and is one-fourth the area of the pregnant corpus luteum at the height of its activity. This decrease in size is associated with a gradual obliteration of the central cavity which is completed by the fifth month, the gland as a whole measuring 12 by 8 by 5 mm. From this period until term, the corpus luteum remains almost stationary in size. The theca lutein cells, which are very prominent in the early months of gestation, diminish in number after the fifth month, disappearing completely shortly thereafter.

In the case presented herewith, the corpus luteum near term was grossly abnormal, in so far as its size was relatively gigantic, measuring 4 cm. in diameter, with an unusually large number of theca lutein cells; the central cyst cavity was almost completely absent, and the size of the mass was attributable to the large number of active luteinized granulosa cells.

Case Report

The patient was a 31-year-old, gravida ii, para i, of Italian extraction, whose last monstrual period was Jan. 12, 1949, and whose expected date of confinement was Oct. 19, 1949. Her previous medical and surgical history as well as her family history were entirely irrelevant. Her first pregnancy terminated uneventfully 2½ years previously. Suppression of lactation was accomplished by the administration of stilbestrol after attempted breast feeding for two days was unsuccessful. At her initial visit, the physical findings were those of a normal 6 to 8 weeks' gestation and the patient offered no complaints. On a subsequent visit, May 21, 1949, at four months' gestation, she pointed out the appearance of a painful lump in the right breast of one week's duration. During a period of four weeks which followed, the lump grew from the size of a "penny" to that of a "baseball," and the pain became progressively more severe. Aspiration biopsy was performed and numerous clumps of cancerous breast epithelium were found. On June 26,

1949, at 24 weeks' gestation, she was admitted to the hospital and a right radical mastectomy was performed. Pathological diagnosis of the breast tissue was "infiltrating duct carcinoma, Grade III; axillary lymph nodes show no metastatic carcinoma." She was discharged from the hospital on July 7, 1949, in excellent condition. Her subsequent prenatal course was uneventful. Because of the diagnosis of carcinoma of the breast,

Fig. 1.—Cut surface of right ovary showing encapsulated mass 4 cm. in diameter with slit-like central cavity.

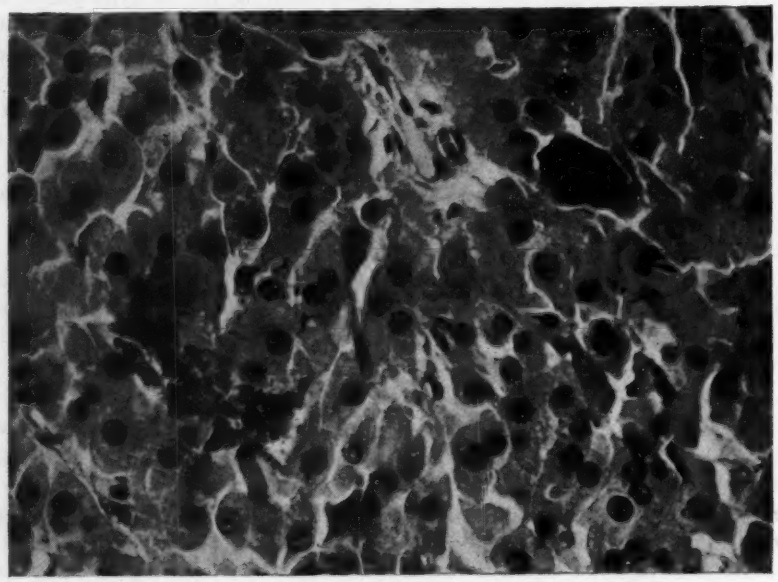


Fig. 2.—Typical granulosa cells of hyperplastic corpus luteum of pregnancy.

it was decided to perform a surgical castration. Therefore, on Sept. 28, 1949, at 37 weeks' gestation, an abdominal hysterotomy and bilateral salpingo-oophorectomy were performed. A living male infant weighing 5 pounds, 13 ounces, was delivered. The right ovary was enlarged to the size of a lemon and appeared cystic externally. Mother and baby were discharged in good condition on the tenth postoperative day.

On a follow-up visit, eight weeks postoperatively, the patient's general condition was satisfactory and there were no complaints. The mastectomy scar was well healed and free of nodulations. There were no axillary masses. The left breast was soft. The abdominal scar was well healed. On bimanual examination, the uterus was well involuted and anteriorly placed. The cervix was high in the vault of the vagina and there were no

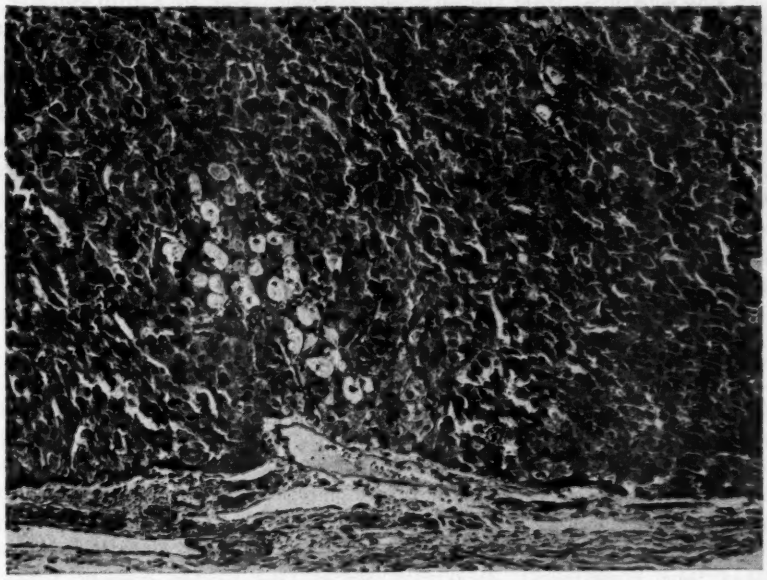


Fig. 3.—Foci of completely luteinized granulosa cells scattered through corpus luteum.

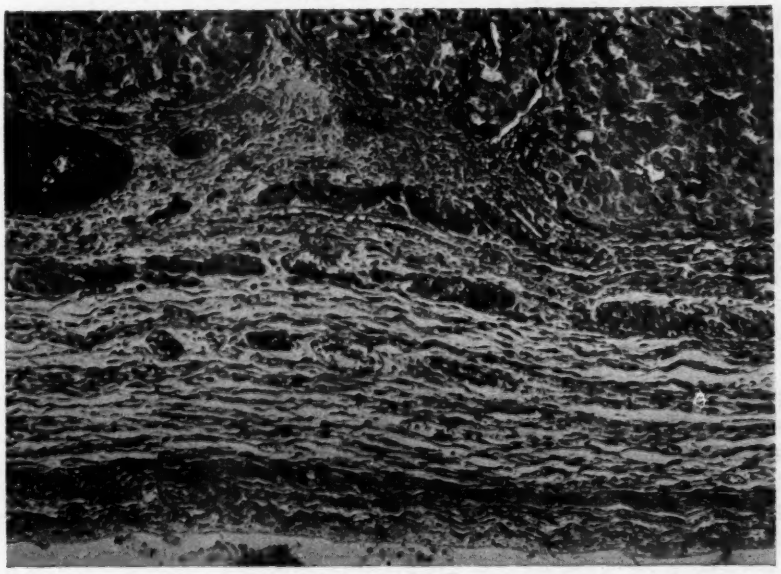


Fig. 4.—Demarcation zone between corpus luteum and compressed ovarian stroma. Paralutein theca cells are seen in strands at the boundary zone.

pelvic masses or tenderness. Subsequent examinations at three months and seven months were essentially negative except for a mild cervicitis which responded readily to cauterization. The vaginal secretion had a pH of 5 and vaginal smears revealed a mild degree of cytological changes associated with castration.

Pathology

Gross: The specimen consisted of both ovaries and Fallopian tubes. The smaller ovary measured 3 by 2 by 1.5 cm., and on section contained numerous small cysts, some of which were filled with blood. The larger ovary measured 4.5 by 4 by 2 cm. On section a large round mass 4 cm. in diameter was seen which bulged above the cut surface (Fig. 1). It was separated from the adjacent ovarian tissue by a thin capsule. The mass was composed of soft, reddish-brown homogeneous tissue with a slitlike, centrally placed cavity.

Histopathology: The mass was composed of uniform, large, polygonal cells containing prominent vesicular nuclei which were rounded to ovoid in shape and presenting prominent centrally situated nucleoli (Fig. 2). The cytoplasm was abundant, acidophilic, and was well delineated. Several groups of cells were found which showed marked vacuolation of the cytoplasm and pyknosis of nuclei (Fig. 3). The mass was separated from the adjacent compressed ovarian tissue by a thin connective tissue capsule. At the boundary zone, groups of cells similar to the bulk of the cells in the mass were found admixed with the spindle elements resembling theca cells (Fig. 4).

Diagnosis: Hyperplastic corpus luteum of pregnancy.

Comment

A search of the literature was made to find similar instances of marked overgrowth of the corpus luteum of pregnancy near term. No reports were available. In addition, the authors contacted personally several leading pathologists of institutions where oophorectomies have been performed for breast carcinoma, and in each instance obtained negative reports as to specific alterations of the corpora lutea. Parker and Aldredge[2] reported 92 cases of breast carcinoma during pregnancy and lactation without ovarian changes other than metastases. Dockerty[3] states that at the present time there is a tendency to reject the thesis that the human corpus luteum is ever the seat of neoplastic transformation.

During the initial phase of study of the surgical specimen, consideration was given to a possible diagnosis of luteoma. However, study of the microscopic slides revealed quite clearly that the histologic appearance of the mass was identical to an early corpus luteum of pregnancy. The occurrence of such a large number of theca lutein cells so near term is abnormal.

Experimental work by Deanesly,[4] who quotes Selye and others, and by Westman[5] indicates clearly that the estrogens are capable of enlarging and maintaining existing corpora lutea. Estrogen injections caused the production of enlarged corpora lutea similar to those of pregnancy in the nonpregnant rat. It is postulated, therefore, that the hyperestrinemia of pregnancy served to stimulate the growth of an incipient breast carcinoma and that this hyperestrinemia also maintained and stimulated the growth of the corpus luteum.

Summary

1. A case of marked hyperplasia of the corpus luteum of pregnancy in association with carcinoma of the breast is presented. It is suggested that the marked hyperplasia was initiated and maintained by the hyperestrinemia associated with pregnancy, the hyperestrinemia also stimulating the growth of an incipient breast carcinoma.

2. A search of the literature has revealed no other reported instances of hyperplasia of the corpus luteum of pregnancy.

References

1. Gilman, J., and Stein, H. B.: Surg., Gynec. & Obst. 72: 129, 1940.
2. Parker, Joe M., and Aldredge, W. M.: South. Surgeon 15: 550, 1949.
3. Dockerty, Malcolm B.: Internat. Abstr. Surg. 81: 179, 1945.
4. Deanesly, R., and Newton, W. H.: J. Endocrinol. 2: 317, 1941.
5. Westman, Axel: Tr. Endocrinology 26: 774, 1940.

1333 President Street

UTERUS DUPLEX WITH TRANSVERSE SEPTUM OF THE VAGINA

M. JAMES WHITELAW, M.D., PHOENIX, ARIZ.

(From Humanity Memorial Hospital)

IN NONE of the few cases of transverse septum of the vagina reported in the literature[1, 2, 3] has there also been a uterus duplex. Because of this rarity and its possible embryological implications, as well as the opportunity which was afforded the author to compare radiopaque media for hysterosalpingography, this case is being presented.

Case Report

Mrs. V. W., a 30-year-old white woman, para i, gravida i, was first seen on June 12, 1949, because of visual disturbances occurring several days premenstrually. Her menarche was in 1934. Menses were regular, 28 to 30 days, with a heavy flow, the duration of which was five to six days, with severe dysmenorrhea. There was severe premenstrual tension. She was married in 1942 and used contraceptives, in spite of which she became pregnant and was delivered by cesarean section in 1944 before going into labor. The exact reason for the section was not determined. On pelvic examination a normal introitus and perineum were seen. No cervix was visualized. A typical-appearing vagina ended in what seemed to be a blind pouch. It was noted on careful inspection, however, that both edges were free and could be sufficiently pulled to one side to reveal the lateral borders of two small cervices. A hysterogram was taken. Because of the technical difficulties involved in trying to place and maintain the cannulae in the two cervices at the same time with the transverse septum present, the first cannula was withdrawn after injection of the radiopaque medium into one side. As there has been a great deal of controversy regarding the effectiveness of a water soluble radiopaque medium versus oil,[4, 5, 6] the right cervix was injected with Lipiodol while the left was injected with a water soluble medium.* The transverse septum acted as a diaphragm against the cervix when the cannula was withdrawn, retaining the medium (Fig. 1).

A uterus duplex was revealed. The patient was operated upon and the thick vaginal septum was easily removed by sharp dissection from the anterior and posterior walls of the vagina. The two cervices were now clearly visible (Fig. 2). Following recovery from the operation, the uterus was again injected with the same two types of radiopaque substances, which on this occasion demonstrated only the bodies of the uteri.

Comment.—It has been stated in various texts[7, 8] that the upper third of the vagina as well as the cervix is embryologically derived from the Müllerian ducts by fusion, only the lower portion being formed by the cloaca. If this concept is correct, it is difficult, in this case, to visualize how one can have a transverse vaginal septum just beyond the two cervices without evidence of fusion of the Müllerian ducts at the level of the cervices unless, as Novak[9] suggests, the vaginal septum could be looked upon as having displaced upward the original Müllerian epithelium.

*The Rayopake used in this study was supplied through the kindness of Hoffman-La Roche, Inc.

The x-ray films leave little room for doubt that a water soluble medium is just as efficient as Lipiodol from the standpoint of radiopacity. This is cited by the advocates of Lipiodol as its main advantage over an aqueous medium.

Summary

A case of transverse vaginal septum with a uterus duplex is described. The embryological significance of this in the light of the origin of the upper third of the vagina is discussed. The injection of Lipiodol into one uterus and an aqueous contrast medium into the other showed no difference of opacity.

Fig. 1.—Hysterosalpingogram showing a uterus duplex previous to operation. Lipiodol was used for the right uterus, Rayopake for the left.

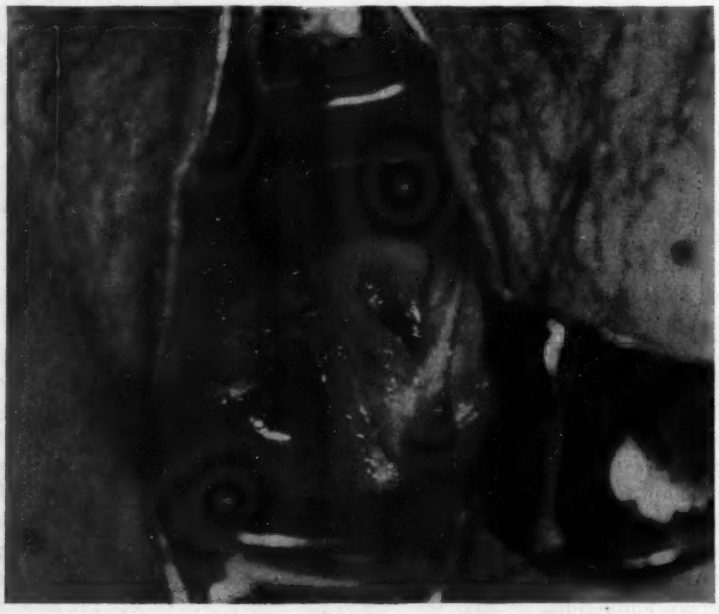


Fig. 2.—Photograph after removal of the transverse vaginal septum showing the two cervices.

References

1. Dannreuther, Walter T.: Am. J. Obst. & Gynec. 47: 827, 1944.
2. Rubin, I. C.: Personal communication.
3. Bayse, J. A., Winslow, A. L., and King, R. W.: Bull. Permenente Foundation 7: 45, 1949.
4. Rubin, I. C.: J. Mt. Sinai Hosp. 7: 479, 1941.
5. Whitelaw, M. James: Arizona Med. 5: 42, 1948.
6. D'Alsace, Jean: J. Mt. Sinai Hosp. 13: 175, 1947.
7. Wharton, Lawrence R.: Gynecology Including Female Urology, Philadelphia, 1943, W. B. Saunders. Company, p. 43.
8. Crossen, Harry S., and Crossen, Robert J.: Diseases of Women, ed. 9, St. Louis, 1948, The C. V. Mosby Company, chap. xiii.
9. Novak, E.: Personal communication.

412 West Roosevelt.

EFFECT OF THORACOLUMBAR SYMPATHECTOMY ON LABOR

LEE M. HERSHENSON, M.D.,* PITTSBURGH, PA.

(From the Montefiore Hospital)

THORACOLUMBAR sympathectomy, an extensive ablation of autonomic nerves, might be expected to produce some appreciable effect on the powers or pains of labor. Few detailed reports on this subject exist. Newell and Smithwick[1] reported fourteen cases of pregnancy following sympathectomy and stated only that three of these patients had "normal labor," one "a short painless labor," and one a labor which was "painless until the head distended the perineum." Austin and Frymire[2] reported in detail a labor in a secundigravida following the Smithwick operation but did not record the character of her first labor for comparison. Such comparison would be helpful in evaluating the effect of the operation on a process which even when normal has a wide range of individual variation. This paper illustrates the effect of this operation by the record of a woman's two labors, one before and one after thoracolumbar sympathectomy.

Case Report

Mrs. T. F. H. was first seen in the outpatient department of Montefiore Hospital in December, 1939, when she was a primigravida six months pregnant. Pregnancy was eneventful except that the blood pressure ranged from 130/80 to 138/90 and the urine contained a trace of albumin.

On March 25, 1940, she began to have rhythmic pains which were mainly in the sides and lower back. When she was admitted to the ward an hour after the onset of pains, the cervix was partly effaced and 2 cm. dilated. The head was high and was presenting occiput right posterior. Pains continued to be only moderate in severity and chiefly in the lower back. After 12 hours the cervix was fully effaced and 4 cm. dilated. Pentobarbital sodium, 100 mg., was given. Five hours later effacement and dilatation were complete, and membranes ruptured spontaneously. Descent of the head continued as a persistent posterior, with contractions active but pains not intense. The duration of the second stage was 3 hours, 40 minutes, delivery being accomplished by low forceps extraction. The third stage lasted 10 minutes.

In 1942 the patient was readmitted to the hospital for dilatation and curettage and replacement of the retroverted uterus with inserion of a pessary. Her blood pressure was 150/110. A Grade 2 systolic murmur was heard at the cardiac apex. The heart was enlarged roentgenographically. The electrocardiogram indicated left axis deviation. Marked albuminuria was present. Blood nonprotein nitrogen was 27 mg. per 100 ml. Two years later, in 1944, she was again admitted for a minor surgical procedure. At that time her blood pressure was 175/110 and urinalysis showed only a trace of albumin.

The patient was admitted to the hospital for the fourth time on March 26, 1947. In the several months preceding this admission she had begun to have frequent headaches, sometimes with vertigo and tinnitus. She had noted an increasing degree of exertional dyspnea and orthopnea and had had a few attacks of paroxysmal nocturnal dyspnea and of precordial pain. She had had no nocturia. No history indicative of previous renal disease could be elicited. Examination on admission showed moderate cardiac enlargement and a Grade 2 apical systolic murmur. No signs of congestive heart failure were present. Blood pressure was 200/130. Ocular fundi showed Grade 2 hypertensive changes, with narrowing and spasm of arterioles. The urine had a trace of albumin and a maximum specific gravity of 1.020 on a concentration test. Blood nonprotein nitrogen was 31 mg. per 100 ml. The

*Present address, 5618 Bartlett St.

amytal test showed a labile pressure which fell to 144/90. Bilateral thoracolumbar sympathectomy and splanchnicectomy were performed (Dr. Y. D. Koskoff) in two stages, on April 7 and May 5, 1947. The sympathetic chain was resected from the eighth thoracic to the second lumbar segment on the left and the ninth thoracic to the first lumbar on the right, the splanchnic nerves were resected bilaterally, and the major portion of the celiac plexus was removed. Convalescence from both stages was uncomplicated. At discharge her blood pressure was 170/110. The eyegrounds still showed some vascular narrowing, but no spasm was evident.

Following discharge the patient continued to have occasional headaches, mild dyspnea on exertion, and palpitation, but to much less a degree than formerly. Her blood pressure ranged from 140/90 to 158/110.

In November, 1948, she became pregnant for the second time. She was admitted to the hospital in her sixth month because of increased frequency of headaches and palpitation. Her blood pressure at this time was 150/90. The retinas showed Grade 1 arteriolar changes. There was no dependent edema or pulmonary congestion. Urinalysis showed a trace of albumin and a maximum concentration of 1.026 on a Fishberg test. The urea clearance was 63 per cent of mean normal. It was decided to allow pregnancy to continue with restriction of activity and of sodium intake. Toward the end of the seventh month she began to have slight edema of the feet and ankles. Her blood pressure ranged from 140/92 to 162/100. In the eighth month nausea and vomiting, which had been present in the first trimester, recurred briefly.

On Aug. 28, 1949, she began to have rhythmic pains in the suprapubic area and lower back. On admission, the cervix was effaced and 3 cm. dilated. The head was at midpelvis, presenting occiput left transverse. Pains increased in frequency but remained mild to moderate in intensity, so no sedation was given. After 5 hours, 45 minutes, cervical effacement and dilatation were complete, and membranes ruptured spontaneously. Ether analgesia was employed during delivery, supplemented by procaine infiltration at the site of episiotomy. The second stage lasted 39 minutes, and the third stage 3 minutes.

Comment

The course of this woman's second labor was moderately swift, the total duration being a little more than 6 hours as compared with nearly 21 hours for her first labor—quite a normal variation between a first and second labor. The extensive neurosurgical procedure had no clinically apparent effect on uterine motility. This may be accounted for by the fact that, although the majority of sympathetic motor fibers to the uterus were cut, there still remained intact sacral parasympathetic fibers and also the ability of the pregnant uterus to contract independently of motor innervation due to the inherent rhythmicity of the myometrium itself.[3]

This patient's second labor was equal to her first in painfulness, too. Sympathectomy interrupted only the sensory fibers for pain from the uterine fundus, which pass by way of the uterovaginal, hypogastric, and aortic plexuses to the eleventh and twelfth thoracic roots,[4] and which are significant only in the initial pains of the first stage. By far the bulk of labor pain is due to lower uterine segment and cervical dilatation,[5] with perineal pain becoming prominent as the second stage proceeds. These pain fibers, which pass to the second, third, and fourth sacral roots, were not touched by the operation. The lack of analgesic effect in the case presented here is in contrast to that noted in two of Newell and Smithwick's cases. It is in agreement, however, with observations concerning labor following resection of the superior portion of the hypogastric plexus (presacral neuroectomy) for relief of dysmenorrhea, following which operations labor is often less painful at the onset but not painless. Failure of any effect in this patient cannot be attributed to too limited extent of the sympathectomy, since it was extensive enough to relieve her hypertensive disease and permit her to tolerate pregnancy subsequently better than might have been expected otherwise.

Summary

The effect of thoracolumbar sympathectomy on labor is illustrated by a report of a case in which this operation was performed for hypertension following a woman's first delivery but prior to her second pregnancy. This extensive interruption of uterine motor and sensory nerve pathways did not interfere with normal labor.

The author wishes to thank Dr. Harold Cohen, Chief of the Department of Obstetrics, Montefiore Hospital, for his guidance and advice.

References

1. Newell, J. L., and Smithwick, R. H.: New England J. Med. **236**: 851, 1947.
2. Austin, B. R., and Frymire, L. J.: AM. J. OBST. & GYNEC. **56**: 805, 1948.
3. Malpas, P.: cited in Lull, C. B., and Hingson, R. A.: Control of Pain in Childbirth, ed. 3, Philadelphia, 1948, J. B. Lippincott Company, pp. 126-127.
4. Cleland, J. G. P.: Surg., Gynec. & Obst. **57**: 51, 1933.
5. Javert, C. T., and Hardy, J. D.: AM. J. OBST. & GYNEC. **60**: 552, 1950.

PRIMARY CARCINOMA OF THE STOMACH WITH METASTASIS TO THE CERVIX

LEON REIDENBERG, M.D., READING, PA.

(From the Community General Hospital)

THE lesion to be described is so unusual as to warrant this case report.

Mrs. B. M., aged 46 years, came to the Gynecology Clinic complaining of intermittent vaginal staining during the preceding two months. She also complained of enlargement of the abdomen, backache, and loss of appetite for the preceding two months.

Catamenia had occurred at age 11 years and she had been menstruating for 3 days at 30-day intervals. She had had four successful pregnancies and had never been operated upon. Her past medical history revealed no serious illnesses other than childhood diseases.

Physical examination of the chest revealed no abnormality. The abdomen was not distended and neither tumors, tenderness, nor rigidity were present. Pelvic examination revealed the uterus to be normal in size, shape, position, mobility, and consistency. The adnexa were neither palpable nor tender. The speculum examination revealed a healthy cervix.

The patient was admitted to the hospital on July 1, 1949, for diagnostic curettage and biopsy of the cervix. At the time of operation, the endometrium appeared grossly normal. The cervix was curetted and a mass of markedly soft tissue was removed from the left wall, resulting in a cavity about 1 cm. in diameter.

Pathologic examination revealed normal premenstrual endometrium.

The cervical biopsy "in semiserial section showed a rather heavy lymphocytic infiltration of the portio. Large sheets of stratified squamous epithelium were present. Some were cut parallel to and some were cut at right angles to the cervix. There was great variability in the size and shape of the nuclei, many of which were large, irregular, and pyknotic. Mitotic figures were seen. There were occasional whirled patterns formed by the mid-zonal layers of the epithelium. Although no actual invasion could be demonstrated, the changes definitely suggested malignancy in widespread areas of the cervical epithelium."

The pathologic diagnosis was carcinoma of the cervix, origin undetermined. The invading epithelium was found to be too undifferentiated for an accurate diagnosis to be made.

On the fourth postoperative day, the patient complained of abdominal pain. For the first time, the abdomen was tender and moderately distended. Survey films of the abdomen suggested a soft-tissue mass in the lower central abdomen but physical examination did not reveal it.

Her condition remained unchanged and on the twelfth postoperative day another flat plate of the abdomen was taken which revealed no evidence of obstruction, free fluid, nor free gas in the abdomen. The mass previously seen was not well outlined and was replaced by a generalized area of increased density.

The patient's symptoms improved. She was discharged on the fourteenth postoperative day and referred for deep x-ray therapy.

Five days later, she was re-admitted to the hospital complaining of severe abdominal distention, abdominal pain, nausea and vomiting. X-ray therapy had not been begun.

Physical examination revealed free fluid within the abdominal cavity and 5,300 c.c. of yellow fluid were drained by paracentesis. Three days later, the fluid had re-formed

and 4,500 c.c. were removed by paracentesis. Paraffin block studies upon the ascitic fluid sediment revealed masses of epithelial cells varying greatly in size, shape, and staining properties. Pyknotic cells and cells with multiple nuclei were seen.

X-ray studies were made and these included a chest examination, intravenous pyelogram, and gastrointestinal series. The chest film revealed "no pathology." The intravenous pyelogram revealed "normally functioning kidneys and a large compression deformity of the bladder apparently due to a soft tissue mass in the pelvis." The swallowing function and esophagus were found to be normal. There was narrowing of the distal cardiac end of the esophagus but barium passed through without difficulty. There was no evidence of residue barium in the stomach but the stomach was rigid and the barium passed through without very much delay. There was no evidence of gastric peristalsis seen and multiple film studies were made which revealed a distorted mucosal pattern involving the entire stomach. The duodenal cap appeared normal and the second and third portions of the duodenum were normal. The six- and twenty-four-hour studies revealed normal progression of the barium column. The barium did not pass through the rectosigmoid junction and the radiologist interpreted this as a constricting lesion or a severe spasm which he was unable to overcome.

X-ray Diagnosis.—Esophagus: normal; stomach: scirrhous carcinoma involving the entire stomach; small bowel: no pathology; colon: constrictive lesion involving the descending colon and sigmoid.

On the ninth hospital day of the second admission, a laparotomy was performed and generalized abdominal carcinomatosis found. The greatest portion of the malignant infiltration was at the stomach. Neoplastic growths were found on the peritoneum at the site of paracentesis. Specimens were taken from the omentum and peritoneal growths and these revealed highly anaplastic tissue. No cell pattern suggestive of squamous origin was present in either specimen.

On the seventh postoperative day, the abdomen was again distended but without evidence of obstruction.

The patient became worse and died on the eleventh postoperative day.

Autopsy Findings.—The peritoneal cavity contained about 100 c.c. of blood-tinged purulent fluid. The great omentum was rolled into a small mass against the greater curvature of the stomach and contained a number of firm white nodules. There were similar nodules in the thickened gastrocolic omentum and throughout the mesentery of the small intestine and in the thickened splenic pedicle.

Genitals: The uterus and cervix were slightly enlarged and moderately firm. On section, the subendometrial muscle was dense, yellowish white, and tough. In the left lateral aspect of the cervical canal, just above the external os, there was a small craterlike cavity about 0.5 cm. in diameter.

Stomach: The proximal one-third of the stomach was thickened, rigid and on section showed a hypertrophied muscular wall.

Small intestine: The small intestine was generally thickened and the serosa congested. The ileocecal valve was rigid due to a thickening of the muscularis of the terminal ileum and of the cecum.

Large intestine: The cecum was considerably distended and from the root of the appendix to the ileocecal valve the wall is thickened, firm, white, and fibrotic. The proximal half of the appendix was dilated to a diameter of about 2 cm. and showed thick grayish-white walls.

Liver: No evidence of metastatic involvement.

Microscopic Examination.—The cardiac end of the stomach showed a greatly thickened wall with a small mucosal ulceration beneath which the mucosal epithelium was bizarre and irregular in regard to size, shape, and staining of its cells. From this point, malignant epithelial cells invaded the greatly thickened muscle wall. Sections from the fundus of the stomach showed a normal-appearing mucosa but the muscularis was invaded by a number of scattered, bizarre, obviously malignant epithelial cells.

Large intestine: Both cecum and appendix showed similar epithelial cells scattered throughout their thickened muscular walls. In the appendix, these malignant cells were also found in the mucosa but appeared to be invading it from the wall.

Lungs: The lungs showed a few peribronchial infiltrations of epithelial cells, obviously malignant, and occurring in small strands and islands resembling those seen in the gastrointestinal tract.

Cervix: Sections from the ulcerated area showed normal stratified squamous epithelium on the external surface beneath which were a number of vascular spaces, some filled with blood and some with malignant-appearing epithelial cells resembling those seen in the intestinal tract.

Diagnosis.—Purulent peritonitis, generalized peritoneal carcinomatosis, carcinoma of abdominal paracentesis puncture, metastatic carcinoma of cervix, metastatic carcinoma of lungs, primary scirrhous carcinoma of stomach, metastatic carcinoma of small intestine, cecum, and appendix, bowel obstruction.

Cause of Death.—Purulent peritonitis due to bowel obstruction and peritoneal carcinomatosis due to primary carcinoma of stomach.

Summary

A case of primary carcinoma of the stomach with metastasis to the cervix is herein reported. The major symptom was vaginal bleeding.

SUPERFETATION

CHARLES E. GAUPIN, M.D., F.I.C.S., LOUISVILLE, KY.

(From the SS. Mary and Elizabeth Hospital)

Mrs. E. P., gravida ii, para i, aged 24 years, had been in good health since her delivery of a 7 pound, 6 ounce male baby on Sept. 14, 1947. Postpartum examination on Oct. 27, 1947, revealed a first degree retroversion, otherwise no abnormalities.

Present Pregnancy.—Prenatal care began June 13, 1950. The last menstrual period was April 1, 1950. There was no nausea or vomiting, nor any complaints. Menses were regular, with a 28-day cycle, 5-day duration, the flow usually heavy for about the first 3 days. The blood pressure was 110/70, weight 118½ pounds, red blood cells 4,680,000, hemoglobin 95 per cent. Vaginal examination showed an enlarged, softened uterus, the fundus between 2 and 3 fingers above the pubis. Diagnosis, pregnancy.

On July 7, at the second visit, the blood pressure was 112/70, weight 119 pounds, urinalysis negative for protein and sugar. The fundus was about 4 fingers above the pubis. Progress was considered normal.

On August 7, at the third visit, the blood pressure was 110/70, weight 122 pounds, urinalysis negative for protein and sugar. The fundus was 2 fingers below the umbilicus. Her condition was good and progress was normal.

On August 12, shortly after arising in the morning, she noticed pain in the back, dull and aching in character and low in the sacral area. This remained rather constant all day and to get relief she had to lie down off and on all during the day. About an hour before retiring she began having a heavy, bearing down feeling in the pelvis and retired earlier than usual because of this. No bloody discharge or other discharge was noted. She did not rest well during the night and this heavy feeling in the pelvis continued all the morning of August 13. Mucoid discharge was noted but it was not blood tinged. About 1 P.M. she began having contractile pains and noted a heavy, mucoid discharge, but no blood. At 3 P.M. a gush of water escaped from the vagina followed by a bloody discharge. She called and I advised her to go to the hospital immediately. I called at the hospital at about 4:30 P.M. The patient had been shaved and the perineum sprayed with Mercresin. The nurse reported contractile (uterine) pains every 6 to 7 minutes with a moderate bloody discharge present. Abdominal examination revealed the fundus two fingers below the umbilicus, about the same as on her last office visit. She was somewhat tender over the entire uterus, but because of her highly nervous state, the exact significance of this was difficult to evaluate.

Vaginal examination revealed an effaced cervix with practically no dilatation. The lower uterine segment was broad, as if the contents were expanding and obliterating the internal os. Since labor was definitely established with no expectation of a viable fetus, and in view of her highly nervous state, morphine sulphate, ¼ grain, was then given hypodermically. Because of a temperature of 102° F., she was given a complete physical examination and a catheterized specimen of urine was sent to the laboratory for immediate examination. Both of these examinations failed to reveal any definite pathology. Because of this temperature she was given 600,000 units of penicillin.

The patient also stated that on August 11 (2 days before admission) she thought she felt life on this one occasion only, none since that time.

While the morphine hypodermic quieted the nervous condition and lessened the severity of the pains, the contractions continued, so that at 6 P.M. 100 mg. of Demerol were given hypodermically. The patient continued to feel contractions.

At 8 P.M. she began hemorrhaging. She was taken to the delivery room, prepared, and draped. She was bleeding moderately and continued to be very nervous and mentally upset, so that it was thought advisable to give her a light cyclopropane and oxygen anesthetic. On

examination a small, soft mass was encountered just inside of the labia. This was easily removed with the gloved fingers and was found to be a mass of decidual tissue enclosing a small sac, containing a fetus. The fetus was about 2 cm. in length, with definite budding of legs and with eye outlines, corresponding to a 6 weeks' fetal formation.

Further examination disclosed a larger fetus, the breech presenting, lying free in the vagina, the uterus having completely expelled it. Placental delivery followed immediately. The time of delivery was 8:45 P.M.

Fig. 1.—Six weeks' fetus removed from sac.

Postpartum temperature was 97.4° F. in the morning. The temperature remained normal up to the time of discharge on the fourth postpartum day.

Specimens were wrapped in saline soaked gauze and the photograph was made the next morning.

Conclusions

A case of superfetation is submitted.

The second fertilization took place when the original conceptus was of about 3 months' duration.

A 6 weeks' fetus and a fetus of 4 months, 13 days, presented for delivery.

714 Francis Building.

MESONEPHRIC CYST OF THE CERVIX

HAROLD E. VELDMAN, M.D., GRAND RAPIDS, MICH.

(From the Department of Obstetrics and Gynecology, Butterworth Hospital)

A MESONEPHRIC remnant cyst 4 cm. in diameter situated on the distal portion of the cervix uteri is considered enough of a rarity to warrant a case report.

The cyst here reported is conceived as having arisen from a Gärtner duct remnant, either an ampullar remnant which extended to the distal surface of the cervix or a displaced remnant of the duct as it turns from the cervix proper to the adjacent vaginal wall. The cyst lining is similar to that of Gärtner duct cysts which commonly are found in the lateral superior walls of the vagina. Here, incompletely surrounded by dense muscular fibers, it developed as unimpeded as vaginal cysts.

Case Report

C. G., white, single, aged 17 years, presented herself for office examination in January, 1950. Her complaint was that one week prior to her last period, which was normal, she had two days of very scanty vaginal bleeding for which she was unable to account. This was the only occasion of intermenstrual bleeding.

Her menarche was at 14 years of age. Her periods had followed a regular 28-day pattern with very slight cramping at each period. Her history in other respects was normal.

Her appearance was that of a normal, well-developed girl, and general physical examination was normal. Vaginal examination revealed a nulliparous introitus. The hymen admitted a small virgin-sized speculum. The vaginal walls were intact and devoid of any bleeding lesion. The cervix was visualized and was remarkable in that a bluish-white cystic structure 4 cm. in diameter covered the cervix. A narrow slitlike cervical os could be identified at the upper left portion about 1 cm. from this margin of the cervix. The tumor had the appearance of vaginal cysts seen in the upper lateral walls of the vagina but was tense to pressure. The right and superior margins of the cyst were surrounded by a narrow cuff of cervical tissue about 2 cm. from the most distal surface of the cyst. The uterine body could be identified in an anterior position, freely movable, normal in size and contour. Adnexa could not be clearly palpated at this examination.

Surgery was performed under Pentothal Sodium anesthesia on April 10. A midline episiotomy was done and the hymen incised for adequate exposure of the lesion. The cervical os was identified as a flattened slit at two o'clock position. Enucleation of the cyst was begun superiorly. Scissors spreading was ineffective because of the dense fibrous attachment of cervical tissue into the wall of the cyst. Sharp dissection was carried out at the cuff-like margin. As this proceeded, the cyst was entered and clear viscous contents of the cyst exuded. After insertion of a finger inside the cyst wall, dissection was facilitated and the cyst was removed completely. After removal, the cervix appeared as if a Sturmdorf conization had been done. The cervical canal now occupied the center of the defect. Closure was done by the Sturmdorf technique. The episiotomy was repaired in the usual manner.

Healing was very satisfactory and a good patent canal was obtained. The patient has had normal menstrual periods since surgery was done.

The pathological diagnosis by Dr. Paul Van Pernis is as follows:

Gross: This collapsed cystic structure was 3 by 2.5 by 1.5 cm. The tissue consisted of dense fibrous tissue with an attached cyst about 2 cm. in diameter. The cyst had a fibrous capsule and a smooth lining.

Microscopic: These tissues had a thick, fibrous wall with scattered regions of hyalinization which surrounded a pocket which was lined with columnar epithelium in shallow folds. Beneath this epithelium there were several glands which were filled with secretion material and lined by columnar epithelium. There were no malignant changes. The glands were like those found in cervical tissues but squamous epithelium was absent.

Diagnosis: Embryonic remnants with cyst formation in cervix.

1418 Plainfield Avenue.

CARCINOMA OF THE VULVA IN A YOUNG WOMAN*

A. F. Lash, M.D., Ph.D., and M. Zibel, M.D., Chicago, Ill.

(From the Cook County Hospital)

PRIMARY carcinoma of the vulva is a disease of elderly women, the average age being about 59 or 60 years (Novak[1]). According to Hunt,[2] it is rare under 40 years of age. Rothschild[3] in a series of 331 cases found the incidence greatest in the decade 61 to 70 years. Kinoshita[4] reports a case in a girl of 14, and 9 other cases have been recorded up to the twenty-fifth year. Taussig[5] in reviewing 155 cases from 1917-1940 reported a 24-year-old patient as his youngest. In Lunin's[6] series of 50 cases from Charity Hospital in New Orleans, 1937-1946, the youngest patient was 23 years old. Folsome[7] found in a series of patients a 24-year-old individual.

The following patient's record merited reporting because of her youth.

G. H., a 26-year-old Negro woman, well developed, 5 feet, 4 inches in height, weighing 125 pounds, and not appearing acutely ill, was referred from the Chicago Intensive Treatment Center and admitted to Cook County Hospital, July 24, 1950. The following history was obtained:

At the age of 11 years, the patient first noted moderate pruritus vulvae associated with a nodule at the posterior margin of the left labium major. Her family physician diagnosed the condition as venereal warts and prescribed topical medications. The lesion disappeared in several weeks but the pruritus persisted.

Four years later the lesion recurred at the same area, was firm and nodular without tenderness but the pruritus became more severe. At this time there was an additional nodule on the perineum near the rectum. Her physician prescribed topical medications and the lesion near the rectum disappeared, the pruritus diminished, but the vulvar lesion persisted.

During the succeeding ten years the patient was treated by a number of physicians with ointments and various topical medications including podophyllin.

In April of 1949, the patient was seen at the Chicago Intensive Treatment Center where two consecutive months of oral sulfadiazine, a course of aureomycin, and topical medications to the lesion were administered.

The patient left the care of this clinic and sought the aid of several private physicians during the next year and was treated with intramuscular penicillin, hormones, vinegar douches, and topical medications.

During this last year, the patient noted the lesion increasing in size, intense pruritus and soreness, and, in April of 1950, small superficial areas of reddening on the surface of the lesion.

In June of 1950 the patient returned to the Chicago Intensive Treatment Center where a biopsy was obtained and sent to the University of Illinois. Another biopsy was taken at Northwestern Medical School.

Surgical history of the patient included an appendectomy in 1942, an operation for intestinal obstruction in 1944, and a myomectomy in 1946.

The patient was married at the age of 16 and divorced three years later. Her menstrual history had been normal and she has never been pregnant.

General physical examination showed no pathologic conditions other than that of the genitals. The abdomen revealed a right paramedian and a midline suprapubic scar.

The left labia majora and minora were marked by superficial areas of ulceration on a lesion 2 cm. in diameter. There appeared to be induration of the surrounding skin extending 1 to 2 cm. about the lesion. Even gentle examination of the labia elicited great pain.

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*Presented before the Chicago Gynecological Society, Oct. 20, 1950.

The inguinal lymph nodes were bilaterally enlarged to pea size.

Blood chemistry, blood counts, urine analyses, and repeated smears for Donovan bodies were negative. Spinal, repeated Kahn, and cardiolipin tests for syphilis were negative. The Frei test was negative.

Biopsy report by the University of Illinois was squamous-cell epithelioma in situ (early) (July 13, 1950).

Biopsy report by Northwestern University Medical School: "There is a difference of opinion in our clinic staff. Some felt the section showed granuloma inguinale and others believed that an intradermal carcinoma was present" (July 15, 1950).

On Aug. 2, 1950, a vulvectomy was performed at Cook County Hospital. A section through the lesion at this time revealed a microscopic picture of an early infiltrating, markedly anaplastic squamous-cell carcinoma.

On Sept. 12, 1950, the inguinal and iliac nodes, and deep inguinal and femoral nodes were resected without evidence of malignancy in the microscopic examinations of these tissues.

The vulvectomy wound healed by primary intention. The right abdominal wound became infected but healed by secondary intention.

The patient left the hospital in good condition.

References

1. Novak, E.: Gynecological and Obstetrical Pathology, Philadelphia, 1940, W. B. Saunders Company.
2. Hunt, E.: Diseases Affecting the Vulva, St. Louis, 1948, The C. V. Mosby Company.
3. Rothschild: Quoted in Teacher, J. H.: A Manual of Obstetrical and Gynecological Pathology, London, 1935, Oxford University Press.
4. Kinoshita: Cited by Teacher.[3]
5. Taussig, F. J.: Am. J. Obst. & Gynec. 40: 764, 1940.
6. Lunin, A.: Am. J. Obst. & Gynec. 57: 742, 1949.
7. Folsome, C. A.: J. A. M. A. 114: 1499, 1940.

RUPTURE OF THE UTERUS ASSOCIATED WITH SPONTANEOUS LABOR AND DELIVERY

WALTER F. DILLON, M.D., AND HERBERT E. SCHMITZ, M.D., CHICAGO, ILL.

(From the Lewis Memorial Maternity Hospital)

THIS 28-year-old Negro woman was admitted to the prenatal clinic on Oct. 3, 1949 (Case History No. 26765). Her last menstrual period was Aug. 17, 1949, and the expected date of confinement was May 24, 1950.

Past History.—Familial, medical, and surgical history were negative. In April, 1939, the patient had a spontaneous abortion at 2 months. In August, 1943, the patient delivered a 5 pound, 14 ounce, male infant spontaneously after a 10½-hour labor with no complications.

Prenatal Course.—Initial examination was within normal limits, as were all laboratory data. Examinations at subsequent clinic visits were normal.

Course in the Hospital.—The patient was admitted to the labor floor at 8:30 A.M., May 21, 1950. The membranes were intact, and rectal examination revealed a 1 cm. dilated cervix, vertex presenting at a –4 station, and fetal heart tones normal. Because of weak irregular uterine contractions, a diagnosis of early labor was made. At 1 A.M. the next day, she began having hard contractions, and after 1½ hours of labor, she spontaneously delivered a living 6 pound, 14 ounce, infant under ether analgesia. Five minutes later, the placenta was delivered by simple expression with a blood loss of 50 c.c. Shortly thereafter, the patient began to bleed moderately and the uterine cavity was explored by the resident physician and no abnormality noted. The uterus responded to Ergotrate intravenously and Pituitrin intramuscularly. At 2:45 A.M., May 22, ten minutes after the placenta was delivered, the patient went into profound shock and blood pressure and radial pulse could not be elicited. Plasma under pressure was administered in each arm while blood was being obtained from the bank, and oxygen was given by mask. After the patient began to receive blood, she showed signs of improvement and at 4:22 A.M. the blood pressure was 60/0. Because the shock condition showed no improvement over the initial response, despite additional blood, the patient was examined under cyclopropane anesthesia. The corpus of the uterus was found to be firm and intact. On the right lateral wall of the lower uterine segment, a defect was palpated that was interpreted as an incomplete uterine rupture. Because bleeding was still active and the patient's condition would not tolerate major surgery, the anterior vaginal wall and bladder were reflected off the cervix, and a straight clamp inserted around each cardinal ligament, incorporating the uterine artery and vein. The bleeding immediately decreased and pressure rose to 70/0. At 8:00 A.M., the patient was receiving her seventh 500-c.c. bottle of whole blood, and the systolic pressure had risen to 102. The patient was prepared for major surgery as some active bleeding was still present. Laparotomy revealed a complete uterine rupture into the right broad ligament. A total hysterectomy was performed as well as a right salpingo-oophorectomy because of large varicosities in the infundibulopelvic ligament. Including the blood administered during surgery, the patient received a total of 5,000 c.c.

Puerperium.—The patient's course was essentially uneventful except for a temperature of 102.4° F. on the evening of the second postoperative day. She received both penicillin and dihydrostreptomycin. Her response was good, and on the ninth day she had been afebrile for 32 hours. She was discharged the following day. On her postnatal visit June 20, 1950, the vagina showed normal length, and a few granulations on the vaginal cuff were cauterized.

Summary of Pathological Report.—Near the internal os on the right side was a defect measuring 5 cm. in diameter. Microscopic examination of tissue from the area of rupture showed degeneration of muscle fibers and areas of hemorrhage.

7449 COTTAGE GROVE AVENUE.

Department of Reviews and Abstracts

Selected Abstracts

Gynecology

Henricksen, Erle, and Murrietta, Thomas: Adenocarcinoma of the Corpus Uteri—A Clinicopathological Study, West. J. Surg. 58: 331, 1950.

Adenocarcinoma of the corpus, although generally considered to be much less frequent than carcinoma of the cervix, actually in private patients occurs in an incidence ratio of one to two. This stands in contrast to the incidence ratio on the wards where it is much less frequent, one to seven. This report has to do with 336 cases of fundal carcinoma.

Parity is not so evident in these patients as it is in carcinoma of the cervix, only 67 per cent of the patients having borne progeny, while in the cervix malignancies 82 per cent were parous. Delayed menopause has been said to be a predisposing factor but in this series it did not appear important although the group did give history of a significant increase in menstrual disturbance during their menopause years. The author is impressed with the large number of fundal carcinomas associated with other uterine pathologic conditions particularly those disease states thought to be associated disturbances in estrogen metabolism such as endometrial hyperplasia, endometrial polyp, uterine myomas, and cervical polyp. These tumors occur during the period of ovarian involution but also at a time when the estrogen production is unopposed by progesterone. They are not necessarily associated with estrogen levels. There are many signs to indicate that these patients harbor some unknown derangement in estrogen metabolism not commonly seen in the menopausal patients who do not develop fundal neoplasms.

Metastasis occurs by direct extension into the parametrium in 45 per cent of the cases coming to autopsy, while spread to the primary chain of lymph nodes occurred in 27 per cent. The most common causes of death are uremia, pyelonephritis, hemorrhage, carcinomatosis, cardiovascular accidents, peritonitis, intestinal obstruction, in the order named. Distant metastasis is most often found in lung, liver, bowel, and ovary. In this series of cases the diagnosis was not made until the autopsy in 15.1 per cent of the cases.

The treatment preferred by these authors is deep x-ray irradiated followed in six weeks by total hysterectomy.

WILLIAM BICKERS

Zilliacus, Harry: The Intravascular Aggregation of Erythrocytes in Certain Gynecological and Obstetrical Conditions, Acta obst. et gynec. Scandinav. 30: Suppl. 7: 348, 1950.

Knisely's technique of direct observation with the capillary microscope of blood flow in the conjunctival vessels was applied by Zilliacus to the study of intravascular aggregation or clumping of erythrocytes in a number of obstetric and gynecologic patients. In healthy, nonpregnant women, there was no erythrocyte aggregation, and a normal pattern of maximum central flow with peripheral lag was observed. During normal pregnancy, there characteristically occurred a gradually increasing tendency toward clumping; this was sometimes, but by no means invariably, associated with increased sedimentation rate.

In late pregnancy toxemia, there occurred maximal erythrocyte aggregation with thrombosis and marked decrease in the rate of capillary blood flow. States of shock associated with surgical trauma and premature separation of the placenta were found to coincide with maximal degrees of erythrocyte clumping. Similar clumping was seen in the conjunctival capillaries of newborn infants of toxemic mothers, but was absent in infants of normal mothers delivered by cesarean section. The injection of heparin into toxemic patients with maximal clumping produced a temporary decrease in the size and tenaciousness of the clumps, and a concomitant increase in flow rate was noted.

This phenomenon was also studied in a group of gynecologic patients, in whom it was found to vary as a function of the traumatic component of the disease or state present. Moderate clumping was observed immediately following endometrial curettage, and for several days afterward. More extensive surgical operations were associated with greater degrees of intravascular clumping, with maximal aggregates being observed in patients with severe sepsis and thromboembolic complications. DOUGLAS M. HAYNES

Per, Bergman: Studies on Ovulation Time, Acta obst. et gynec. Scandinav. **30**: Suppl. **7**: 292, 1950.

Although carefully kept basal temperature curves are useful in distinguishing between ovulatory and anovulatory cycles, they do not determine the exact time of ovulation, since some time usually elapses between ovulation and the onset of active progesterone production as indicated by a shift in the basal temperature from a lower to a higher level. It has been found that determination by biologic methods of estrogen excretion levels constitutes the most exact available method for estimating time of ovulation, with maximum estrogen excretion being observed about two days before the premenstrual rise of rectal temperature. Unfortunately, this method is overcumbersome for extensive use. Bergman has developed a method of determining intrauterine temperature by means of a thermoelectric attachment incorporated into a uterine sound. Preliminary data collected in this way show a pronounced drop in intrauterine temperature which coincides with maximum estrogen excretion levels, and which precedes by two days the expected premenstrual rise of the rectal temperature. This method is less readily influenced by external adventitious factors than the rectal method, and would appear to furnish a reliable index of the time of ovulation. DOUGLAS M. HAYNES

Labor, Management, Complications

Baskin, M. J., and Crealock, F. W.: The Management of Cervical Spasm With Dihydroergotamine Methanesulfonate (DHE-45), West. J. Surg. **58**: 302, 1950.

Hydrogenation of the natural ergot alkaloid ergotamine results in the production of a new compound, Dihydroergotamine (DHE-45). It has been used for some time in the treatment of migraine to replace the old alkaloid which has some undesirable side effects. The drug has its effect primarily on the smooth muscle of the arterial vascular system but is also mildly oxytocic to the myometrium although its effect is slight compared to that of ergonovine.

Relaxation of the rigid cervix has been sought by the use of various sympatholytic drugs of the atropine family but always without avail. Indeed, many of the so-called spasmolytics recommended for the spastic unterine muscle may actually be followed by increased basal tone of the myometrium. The innervation, as well as the intrinsic muscle behavior of the myometrium, is not comparable to that of smooth muscle elsewhere such as that of the intestinal tract. More and more evidence has accumulated in recent years to support the belief that uterine muscle dyskinetics including cervical spasm may be related to vascular disturbances and it is for this reason that this new drug holds special interest in relation to the treatment of cervical spasm.

The report deals with the treatment of fifty consecutive primiparas with DHE-45. The drug was administered intravenously from a sterile ampule in a dose of 1 mg. It was given when the cervix was 4 to 5 cm. dilated. In a few patients who had not received previous sedation some intestinal cramps occurred, so in these patients the DHE-45 was accompanied by a dose of Demerol, 50.0 mg. Following the administration of the DHE-45 there occurred almost consistently an increased rate of contractions but no prolongation of contraction time. A single dose was usually all that was required. Comparing the treated group with a like number of controls revealed a reduction in duration of the second stage from one hour forty-eight minutes to 26.7 minutes. The drug was even employed in several cases of pre-eclampsia with no untoward results. No elevation of blood pressure occurred, fetal distress did not occur after its administration, nor were there any lacerations of the cervix. The drug has apparent value in hastening the second stage through a dual action: increased frequency of fundal contractions and relaxation of the cervix.

WILLIAM BICKERS

Arnott, Phillip H., and Nelson, Donald R.: A Comparison of Elder and Younger Primipara, West. J. Surg. **58**: 535, 1950.

A report on the experience of a lone obstetrician with 9,600 personally supervised private deliveries over a period of 27 years is a significant contribution. Interesting although this article is from the technical standpoint it is also rich in human interest, recording as it must the spirit of the profession in adapting itself to the over-changing concepts of what constitutes good obstetrical practice over the tumultuous years of the last quarter century.

An incidence of elderly primiparas of 3.6 per cent, the elderly primipara being the one who delivers her first progeny in her thirty-sixth year or beyond, is recorded in this series. Statistics from large clinics admitting patients from low-income families show an incidence of about 2 per cent or less. It is emphasized that the patients in this group were all private patients. The most advanced ages were 45 and 46 years in two patients, while the great majority of the 346 elderly primiparas were close to 36 years of age. The author compares his experience with the elder group to that with the group whose ages ranged from 18 to 29 years and again makes a comparison with his experience in handling those very young primiparas whose ages were under 18 years.

It becomes immediately apparent to one reading this report that both the medical and obstetrical complications mount with advancing age and it is these complications, notably the former, that account for the higher maternal and fetal mortality in the older group. For example, the toxemias, cardiac disease, and syphilis become more common with advancing years, and placenta previa, abruptio, pyelitis, myomas, and Parkinson's disease were seen only in the oldest group. Pre-existing hypertension and chronic nephritis were seen only in the older patients. The incidence of contracted pelvis was three times more common than in the younger group although not so common as in the very young women (18 years or less). Spontaneous delivery occurred only slightly less frequently in the older group (52.02 per cent as compared to 65.6 per cent) but it is pointed out that about one-half of all patients are delivered by elective outlet forceps anyway. Trauma to the perineum was much more frequent in the very young than the very old, in spite of the fact that occiput posterior positions were much more common in the older patients. The cesarean incidence in the older group approached 9 per cent while the over-all incidence for the entire group of patients was 4.3 per cent. The average duration of labor was about the same in all groups, the primiparas being in labor usually about seventeen to eighteen hours. The weights of the babies were not dissimilar. In the elderly group, however, the fetal deaths climbed to 8.9 per cent. There were five maternal deaths, of which four occurred in the older group.

It cannot be denied that the hazard of childbearing in the primipara mounts with age but the risk is not so disproportionate as one might think when the patients received good obstetrical care.

WILLIAM BICKERS

Mammary Glands

Raven, Ronald W.: Cancer of the Breast Treated by Oophorectomy, Brit. M. J., p. 1343, June 10, 1950.

Raven records a case report of a 50-year-old woman who had a carcinoma of the left breast with multiple metastases to the left axilla, the left supraclavicular region, and to the skin over the right shoulder, the left arm, the chest wall, and the right loin. The observation that these various masses enlarged immediately prior to menstruation led to the decision to perform bilateral oophorectomy. All masses disappeared six months after this operation and the patient was observed for 22 months without recurrence.

There is a historical review of the effects and relative merits of oophorectomy and x-ray castration in carcinoma of the breast. Raven concludes that surgery is more effective than irradiation. He further suggests that a periodic assay of urinary estrogen be made and that if an increase is shown, treatment by androgen should be instituted.

WILLIAM F. FINN

Miscellaneous

Reid, Duncan E., Walter, Carl W., and Buck, Ann S.: Surgical Scrubbing With pHisoderm G-11 as Applied to a Maternity Hospital, Surg., Gynec. & Obst. 91: 537, 1950.

In an effort to test the value of pHisoderm G-11 in a maternity hospital the authors investigated its effectiveness on personnel in the hospital. This personnel included residents, medical students, and surgical nurses. The authors were able to show that pHisoderm is an effective agent for reducing the skin bacteria of the hands after a ten-minute scrub. They were also able to show that the reduction in the bacterial count persisted longer following scrubs with pHisoderm than after scrubs with surgical soap. In addition, they demonstrated that repeated use of pHisoderm makes effective a very much shortened surgical scrub. These latter two findings have been generally accepted. However, the superiority of pHisoderm over surgical soap for one scrub has not been proved, and, as a matter of fact, Dr. Reid's tables do not show any statistically significant difference between pHisoderm and surgical soap in this category.

LOUIS M. HELLMAN

Newborn

Cochrane, J. B., Malone, R. H., and Dunsford, I.: Kell-Cellano Blood Group System in Pregnancy and Transfusion, Brit. M. J. 2: 1203, 1950.

A new antigen-antibody system (Kell) and the newer Cellano antibody, although unrelated to the Rh system, are capable of producing hemolytic disease of the newborn. It has been demonstrated that these genes are alleles and suggested they be designated K and k to indicate the presence of the Kell and Cellano genes, respectively. Some 18 examples of anti-Kell have been observed and the calculated frequency of the genotypes KK, Kk, and kk among white Americans is 0.2 per cent, 8.6 per cent, and 91.2 per cent, respectively.

The authors describe in detail an instance of anti-Kell discovered at the Sheffield Blood Transfusion Centre. They have found the Kell antibody peculiar in reacting in saline and with antihuman globulin, but not reacting in human serum or bovine albumin.

The work of these and other investigators indicates that Kell antibody is of considerable clinical importance as a cause of transfusion reactions and of hemolytic disease of the newborn. The presence of the antibody cannot be detected by routine cross-matching techniques but is demonstrated by means of the indirect Coombs test.

JOHN T. COLE

Kirby, A. C., Hall, E. G., and Coackley, W.: Neonatal Diarrhoea and Vomiting, The Lancet, p. 201, Aug. 5, 1950.

Two outbreaks of neonatal diarrhea in a British maternity-nursery unit are described. In the first outbreak the disease was characterized by vomiting, diarrhea, anorexia, toxemia, and a tendency to relapse. *Bacterium coli* D433 was found in the stools, and the mortality rate was 43 per cent. In a second outbreak the infants developed diarrhea, very little vomiting, and no relapsing tendency. *Bacterium coli* D433 could not be isolated from stools, and there were no deaths.

It is felt that *B. coli* D433 is not a normal intestinal organism in newborn babies and infants. In a series of 370 infants under 1 year of age it was found in 2 per cent, and in another series of 380 it was not found at all. During the outbreak the organism was found in occasional unaffected contact infants. This might suggest that the disease depends on a symbiosis with a second agent, but in none of the reported outbreaks where *B. coli* D433 was isolated was there any other bacterium or virus. Adult volunteers developed diarrhea after swallowing cultures of this organism. It was first isolated by Bray (1945), who termed it *B. coli* (var. neapolitanum), and has since been reported in several other outbreaks of neonatal diarrhea.

IRVING L. FRANK

Editorial: Anoxia in the Foetus and Newborn, The Lancet, p. 19, July 1, 1950.

Anoxia before and during birth is a major cause of stillbirth, neonatal death, and cerebral damage. Fetal anoxia is usually anoxic anoxia due to (a) reduced oxygen tension in maternal blood (asphyxiating anesthetics, fall in maternal blood pressure), (b) systemic maternal disease (anemia, heart failure, pneumonia, etc.), or (c) interruption of placental transfer (uterine tetany, placental infarction, cord accidents). To these causes must be added neonatal apnea, which may be secondary to anoxia (as with high concentrations of nitrous oxide), or to narcosis (as with analgesic drugs or narcotizing anesthetics).

Respiration normally begins in a controlled rhythm. Gasping is the most primitive respiratory form, and its presence means respiratory depression. The manner of onset of respiration is a good index to the state of the central nervous system, and a record may be of future importance. Premature infants commonly show alternate hyperpnea and apnea, even though arterial oxygen saturation is normal. This condition is correctible by giving 100 per cent oxygen, which may reflect a defective form of oxygen metabolism in the premature.

Providentially, the newborn infant can survive anoxia longer than in later life, because of (a) a low cerebral metabolic rate, and (b) a faculty of anaerobic metabolism, with an end point of carbohydrate metabolism short of carbon and water. However, in the survivors, the central nervous system has been the most vulnerable point. Occult damage may be responsible for cerebral palsy, mental defects, or personality disorders.

IRVING L. FRANK

Steiner, Morris, and Pomerance, William: Studies on Prematurity. II. Influence of Fetal Maturity on Fatality Rate, Pediatrics 6: 872, 1950.

This is a report of 791 premature infants born at the Jewish Hospital in Brooklyn, N. Y., covering the five-year period from 1945 to 1950. Only babies weighing up to 2,250 Gm. were included in the study and no exclusions were made on the basis of "nonviability." In order to eliminate small errors the cases have been grouped into gestation periods differing from each other by four weeks.

The data were analyzed to determine the significance of fetal maturity and the magnitude of birth weight as factors influencing survival. The fatalities among 637 babies born of single births were 140 deaths, or 21.9 per cent. For the group of 29 weeks or less the fatality rate was 82.1 per cent; for the group from 30 to 33 weeks it dropped to 23.5 per cent, while in the group from 34 to 37 it dropped to 6.4 per cent, and in the group from 38 to 40 weeks to 5.7 per cent.

Of 154 babies born of multiple births weighing less than 2,250 Gm., 16 died, giving an over-all fatality rate of 10.4 per cent, as compared with an over-all fatality rate of 21.9 per cent for babies born of single births.

It was found that for a given weight group, the fatality rate varied inversely with the length of the gestation period. The outlook for the infant improved in proportion to the degree of its maturity.

Premature infants born of multiple births had a lower over-all fatality rate than those born of single births. This was directly attributable to the greater maturity of babies born of multiple births.

JAMES P. MARR

Brockway, George E., Reilly, Edward T., and Rice, Margaret M.: Premature Mortality. An Analysis of 518 Cases of Prematurity With a Comparison of Negro and White Races, J. Pediat. 37: 362, 1950.

The purpose of this paper is to present the mortality in 518 premature infants born at Kings County Hospital, Brooklyn, N. Y., during the months from January through December, 1949.

It was found that the incidence of prematurity among 3,872 patients was 20 per cent for the Negro race and 15.5 per cent for the white race.

The total premature mortality for the year 1949 (518 babies) was 12.7 per cent. The causes of death are listed and compared with the causes of death at Charity Hospital in 1942. The effect of chemotherapy is evidenced by the lowered mortality due to infection.

A brief outline of the premature routine at Kings County Hospital is given.

JAMES P. MARR

Silverman, Jacob J., and Werner, Max: Fatal Paroxysmal Tachycardia in a Newborn Infant With the Wolff-Parkinson-White Syndrome, J. Pediat. 37: 765, 1950.

The authors state that cardiac arrhythmia in infants may be more frequent than the literature indicates, and many unexplained complications including sudden death may be on the basis of unrecognized paroxysmal tachycardia.

They report a 10-day-old male child who developed intermittent cyanosis, rapid respirations, restlessness and tachycardia. An electrocardiogram disclosed a supraventricular tachycardia with a ventricular rate of 300 per minute. An attempt to abolish the abnormal rhythm by pressure on the carotid sinus was not successful. Digitalis likewise was not successful.

However, in desperation, 0.5 mg., of Mecholyl dissolved in physiologic saline was administered intravenously. The heart rate dropped to 150 per minute. Periodic cyanosis and tachycardia continued until the baby was discharged on the twenty-fourth day, receiving 1 drop of tincture of digitalis twice a day.

Two months later the baby was readmitted because of intermittent cyanosis, labored breathing, and abdominal distention. The infant at this time demonstrated obvious signs of advanced congestive circulatory failure with a heartbeat averaging 300 per minute. In spite of adequate therapy this baby died. No autopsy was performed.

The authors state that in the differential diagnosis of tachycardia in infants, the Wolff, Parkinson, and White syndrome should be kept in mind as definite diagnosis can be made only from the electrocardiogram. It should be emphasized that if electrocardiographic studies are limited to the paroxysms of tachycardia without further investigation when the heart rate is slower, the diagnosis of Wolff-Parkinson-White syndrome will be ignored.

The therapeutic approach to this latter syndrome is outlined. Once a diagnosis of paroxysmal tachycardia is established, effective measures to restore the normal rhythm should be immediately instituted. If the tachycardia is of the supraventricular type, vagal stimulating drugs should be given. The authors prefer Mecholyl because of the rapidity of action and stronger vagal action. They admit that it is dangerous when given intravenously. It has

been postulated that quinidine sulfate has a greater affinity for the anomalous pathway in the Wolff-Parkinson-White pattern, depresses it, and thus allows transmission of the sinus impulse through the normal pathway.

The authors suggest the more frequent use of electrocardiograms in infants, both during and after paroxysms of tachycardia.

An extensive biography is appended.

JAMES P. MARR

Belnap, W. Dean, McKhann, Charles F., and Beck, Claude S.: Cerebral Birth Injury in Retrospect, J. Pediat. **37**: 326, 1950.

This report from the Departments of Pediatrics and Surgery, Western Reserve University School of Medicine, and the Babies and Childrens Hospital, Cleveland, Ohio, deals with cerebral birth injuries.

The authors of the article subjected to analysis 419 children with mental retardation, convulsive disorder, and cerebral palsy, singly or in combination. The ages of these children ranged from 8 months to 14 years.

Over one-half of the patients gave a history suggestive of birth injury while in about one out of six cases the difficulty could be traced to postnatal injury on a traumatic, infectious, or degenerative basis. Mental retardation was found in 89 per cent, convulsive disorders in 47 per cent, and cerebral palsy in 42 per cent of the patients.

Cephalopelvic disproportion is one of the major causes of cerebral damage during the natal process.

With the increasing use of forceps, evaluation should be made of the possible injuries complications resulting from instrumentation. Eastman has found that high forceps carry a 65 per cent mortality and midforceps operations a 30 per cent mortality to say nothing of morbidity.

Careful examination of the histories of the 37 behavior-problem children revealed a significantly higher incidence of a story suggesting birth injury than is true of the normal population. Such a history of a traumatic birth injury is reported in 36 per cent of these children and 8 per cent had a story of postnatal injury. The evidence suggests that birth injuries may be a major factor in their causation.

JAMES P. MARR

Silver, Henry K.: Mediterranean Anemia in Children of Non-Mediterranean Ancestry, Am. J. Dis. Child. **80**: 767, 1950.

Cooley and Lee in 1925 described a series of patients with anemia, splenomegaly, and changes in the bones which made up a disease entity that became known as "Cooley's anemia," "Mediaterranean anemia," "erythroblastic anemia" or thalassemia.

The disease is primarily found in the offspring of families native to areas adjoining the Mediterranean Sea. It is characterized by its familial nature, the presence of "target cells," a blood picture which is hypochromic and microcytic, conspicuous variation in the size of the red cells and increased resistance of the erythrocytes in hypotonic sodium chloride solutions. However, certain variations have been observed in this disease picture, and it is the purpose of this communication to report a series of cases of major and minor forms of Mediterranean anemia occurring in children of non-Mediterranean ancestry.

The first patient reported was the only child of Chinese parents both of whom were born in Canton, China. The second patient was the child of a white American woman of French extraction and of a 34-year-old Filipino who had been born in the Philippine Islands. Three children of this family had mild hypochromic, microcytic anemia which did not respond to iron medication.

The third family was of Mexican extraction. The parents were unaware of any intermarriage in their ancestry with non-Mexicans. The fourth family was Chinese, the father from Canton and the mother from Fresno, California.

Complete histories of these children and their families were given in detail.

The author quotes Caffey, that "persons with mild Mediterranean anemia might reach adult life and constitute the source of transmission of the disease." Angelini and Caminopetros were also of the same opinion.

At present, it is believed that the disease is due to an anomaly of the red blood cells which is inherited as an incomplete recessive or incomplete dominant characteristic. In the person who is heterozygous, there usually is an absence of symptoms and the condition can be diagnosed only by a careful examination of the blood. However, when the anomaly is inherited from both parents, the homozygous person presents the manifestations of the serious disorder described by Cooley and Lee.

Although the disease in both its major and its minor forms is commonest in people from the area surrounding the Mediterranean Sea (especially Italy, Greece, Syria, and Armenia), an increasing number of cases is being reported in non-Mediterraneans—in persons of Argentinean, Chinese, Egyptian, English, Filipino, French, German, Indian, Spanish, and Turkish ancestry.

The cases herein reported illustrate further that Mediterranean anemia in both its major and its minor forms is not restricted to patients of Mediterranean origin.

Of interest is the report of Caminopetros who studied the family trees of a large group of persons with Mediterranean anemia in eastern Greece and brought out the surprising fact that the ancestry of these Greeks included some Chinese who had migrated to Asia Minor. It has been suggested that this might account for the "Mongolian eye" noted in some cases.

JAMES P. MARR

Pregnancy, Complications

Tew, W. P., and McAlpine, H. T.: Eclampsia Treated With Cortisone, Canad. M. A. J. 63: 287, 1950.

A case of eclamptic toxemia with convulsions is reported. The patient, a 34-year-old primigravida, with inadequate prenatal supervision of her own election, was admitted to the hospital in the thirty-sixth week of her gestation with edema, headache, blurred vision. The blood pressure was 220/130 and the urine gave confirmation of the obvious diagnosis with casts and much albumin. She went into labor while under conservative treatment which consisted of the usual magnesium sulfate and hypertonic glucose and when the cervix was 2 cm. dilated the amnion was ruptured surgically. A generalized convulsion occurred a little later, which was treated by intravenous Sodium Amytal. A second convulsion occurred, and so, under continuous spinal anesthesia, a cesarean section was done with the reward of a living fetus. The mother, however, did poorly after operation, deteriorating progressively until she appeared to be in extremis. No further convulsions occurred after delivery but she went into collapse from which recovery appeared more and more remote. She was given 300 mg. of cortisone and promptly the urinary output increased, the pulse began to drop in rate and rise in volume, and she went on to recovery except for the residual of renal damage. Lactation did not occur. This is significant because it is felt by some that the collapse following even in the wake of normal deliveries may be due to anterior lobe pituitary failure and substitution at the adrenal cortical level may well be lifesaving.

WILLIAM BICKERS

Stern, Bruce D.: Fluid Balance and Electrolyte Studies in Toxemias of Pregnancy, West. J. Surg. 58: 344, 1950.

Water metabolism continues to be the fulcrum around which revolves most of the thinking relative to the etiology, pathologic physiology, and treatment of the toxemias of pregnancy. In 100 cases of eclampsia treated by the author between 1938 and 1946, there was a significant correlation between fluid intake, low urinary output, and maternal and fetal mortality. Those cases which terminated fatally during this period had an

average 24-hour fluid intake of 1,384 c.c. and an output of 638 c.c. while the recovery group had an average intake of 2,106 c.c. and an output of 1,782 c.c. In a more recent series of patients with severe pre-eclampsia and eclampsia a system of hydration therapy employing distilled water has been used. This treatment is based on the knowledge that the toxemias have a more than physiologic sodium retention which results in abnormal water retention and by administration of distilled water it is possible to "wash" this sodium from the tissues. In 53 patients with toxemia given distilled water in a volume of 2,500 c.c. daily, there was no maternal and no fetal mortality. Obviously this means little unless it is known what type of cases were under treatment. However, the author contends that so long as a negative sodium balance is maintained peripheral and pulmonary edema subside. He does warn against the administration of large fluid volume in patients with pulmonary edema, he prefers to wait until the lungs have cleared before starting the hydration therapy. He also states that large fluid intake should not be given to patients who are unable to concentrate the urine beyond 1.010. It should be recalled that blood sodium values are no indication of how much sodium the patient is storing in the intercellular spaces; however, serial determinations which show a persistent drop in sodium levels are significant especially when this drop follows in the wake of a slight rise. This indicates that sodium is being pulled from the tissue spaces and is finding its way to the kidneys. Hematocrit determinations are most helpful in following the hydration treatment as the packed cell volume gives accurate information as to the status of the patient's hydremia.

The discussers of this paper raised many doubts on many of the points made. It was said that the statement of the author to the effect that there is a positive tissue sodium balance in the toxemias can be denied on the basis that all retained sodium can be accounted for in the placenta and amniotic fluid. The work of Dieckmann was quoted to the effect that he had given sodium chloride intravenously in large doses to pregnant patients without producing symptoms of toxemia, even to pre-eclamptics it was given without exacerbating their syndrome. We are left to yet surmise and wonder on the toxemias of pregnancy.

Bichel, Jorgen: Hodgkin's Disease and Pregnancy, Acta Radiol. 33: 427, 1950.

The author carefully reviewed the literature and found adequately detailed reports of 46 women with typical Hodgkin's disease complicated by pregnancy. This paper summarizes the case histories of 11 additional patients who were treated at this clinic. In 10 of these the diagnosis of Hodgkin's disease was clear; however, in one case the diagnosis might be questioned.

It would appear from the 11 cases reported that Hodgkin's disease is not adversely affected by complicating pregnancy. Many of the patients felt better during their pregnancy than before. Further, there were no difficulties encountered at delivery, nor did postpartum hemorrhage occur. In some cases, immediately post partum, acceleration of Hodgkin's disease took place with a fatal outcome. Nevertheless, it is very difficult to evaluate the influence of pregnancy on Hodgkin's disease because of its capricious nature. The author concludes that Hodgkin's disease is no indication for interruption of pregnancy.

HERBERT J. SIMON

Sterility, Contraception, Fertility

Holman, Albert W.: Hysterosalpingography in the Study of Sterility, West. J. Surg. 58: 523, 1950.

All too much emphasis has been laid on the interpretation of hysterosalpingograms in terms of tubal patency or occlusion and insufficient consideration given to equally important sterility factors in the uterus. Little consideration has been given to the contours of the cervical canal because, in the opinion of the author, the commonly used long cannula tip precludes proper filling of this essential structure with the contrast medium. The

use of a short, all-metal cannula such as that shown in the illustration accompanying the article permits more satisfactory delineation of the cervical canal and the uterine cavity. It broadens the scope of hysterosalpingography to the study of clinical states not necessarily related to sterility such as dysmenorrhea, abnormal uterine bleeding, ectopic pregnancy, adenomyosis, and pelvic pain of unknown etiology.

Uterine infantilism, it is said, cannot be diagnosed clinically because the diagnosis depends not upon the size or shape of the uterus but upon the relation of cervical to fundal length. It is also emphasized that the infantile uterus frequently shows various cervical abnormalities such as stricture, pouching, or distortion. Such anomalies in the cervical canal, although they do not necessarily impair patency, and menstruation may occur without obstruction, nevertheless interfere in some yet unknown manner with spermigration. These various cervical anomalies are well illustrated in a series of excellent radiographic prints. Hyperplasia of the cervical as well as the uterine mucosa can be demonstrated by hysterosalpingography. Endometrial polyp and intramural fibroids which impinge on the uterine cavity can be readily diagnosed.

A study of 350 hysterosalpingograms revealed evidence of cervical pathologic conditions in 86. There were polyps, strictures, stenoses, and anomalies in size of the canal. The Fallopian tubes were diseased or absent in 75 patients. Evidence of uterine infantilism was diagnosed in 19. In the entire group of 350 patients there were 152 who were considered suitable for treatment. These were subjected to indicated treatments such as dilatation for cervical strictures, removal of polyps, stilbestrol for uterine infantilism (which the author feels is highly effective treatment) and in the treated group there occurred 71 pregnancies. WILLIAM BICKERS

Toxemia

Govan, A. D. T., and Mukherjee, C. L.: Maternal Toxaemia and Foetal Ovarian Activity: Preliminary Observations, J. Obst. & Gynaec. Brit. Emp. 57: 525, 1950.

This is a study of the gross histological findings in the ovaries of 58 stillborn infants; in 25 cases the mother had had some degree of toxemia during the pregnancy; in the other 33 cases the stillbirth occurred at full term and was due to other causes. Signs of follicular maturation were found in the ovaries of 23 of the 25 stillborn infants of toxemic mothers; four types of follicular maturation were found in the ovaries of these 23 infants: early maturation, advanced maturation, cystic atresia of follicles, theca luteinization. In 29 of the 33 control cases (nontoxemic stillbirths), there was no evidence of follicular maturation; in 2 cases there were signs of early maturation in the deep cortex, and in the other 2 cases more advanced changes; in one of these 2 cases, the mother later developed diabetes. From a study of these cases and a review of the literature on the relation of gonadotropin to ovarian activity, the authors conclude that the changes found in the ovaries of the stillborn infants in cases of toxemia are due to gonadotropic stimulation, related to the high concentration of gonadotropins usually found in the blood in toxemic patients, and these gonadotropins are of pituitary rather than of chorionic origin. In the case in which the mother subsequently developed diabetes, it is suggested that both the ovarian changes in the fetal ovaries and the subsequent development of diabetes were indications of anterior pituitary hyperactivity. HARVEY B. MATTHEWS

Vaginal Infections

Bender, S., and Jeffecoate, T. N. A.: Vaginitis Emphysematosa, J. Obst. & Gynaec. Brit. Emp. 57: 432, 1950.

The authors report 2 cases of vaginitis emphysematosa; one of the patients was a nulliparous woman, 33 years of age; the other a multigravida, 41 years of age. Both patients were pregnant when first seen. In the first case, vaginal examination showed a nodu-

lar mass on the upper anterior vaginal wall; two small specimens were subsequently removed from this mass and were found to contain cysts that were filled with air or gas; the condition was not recognized at this time (in 1942). The vaginal condition cleared up entirely when the patient was kept at rest and the pregnancy proceeded normally to term. In the second case observed several years later (in 1949) the patient had noted painless vaginal bleeding for ten weeks. On examination the os was found to be patulous, and there were cystic swellings found on the cervix and the upper vaginal wall. Abortion occurred when the patient was anesthetized for further examination. This showed the cysts to be tense, discrete, and noncrepitant; the diagnosis of vaginitis emphysematosa was confirmed by microscopic examination. This condition is rare as is shown by a review of the literature; the 2 cases reported apparently are the first to be described in England for more than fifty years. In the great majority of reported cases, the women were pregnant and symptoms were slight. The nature of the gas that fills the cysts is not known; giant cells line the smaller cysts but are partly desquamated or compressed in the larger cysts, and in very large cysts may be entirely absent. The etiology of vaginitis emphysematosa has not been determined.

HARVEY B. MATTHEWS

Erratum

In a review by R. A. Bartholomew of the symposium on *Toxemias of Pregnancy,* edited by Dr. J. Hammond, Professor F. J. Browne, and G. E. W. Wolstenholme, in the May issue of the JOURNAL, the second sentence on page 1188 should read: "Falkiner, late Master of the Rotunda, in Dublin, in emphasizing this fact, was admonished to 'investigate this matter afresh and with an open mind.' "

Correspondence

Controlled Hysterosalpingography: Comment on Case Report

To the Editor:

In the January, 1951, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Karshmer and Stein reported a case complicated by "Oil Embolism During Hysterosalpingography."[1] This report recalled similar ones described by Ingersoll and Robbins[2] and Titus[3] some four years ago. My comments on these latter publications can be found in the JOURNAL soon afterwards.[4]

Each time such a complication is reported, ultraconservatives will point to an unfortunate experience and suggest that the technique be either limited in its usefulness or, more likely, completely abandoned. In order to offset criticism that has already occurred in certain medical circles, as a result of Karshmer and Stein's article on hysterosalpingography, I must again take up my pen.

At the very outset, it must emphatically be stated that the *technique* of modern hysterosalpingography is not at fault: it is rather the *individual* performing such procedures who is usually at fault. One would not condemn the use of the automobile simply because there are too many reckless drivers. Similarly, let us not condemn hysterosalpingography because a few investigators take unnecessary chances and risks in its performance.

In the instance of Karshmer and Stein, these reporters state that iodized oil intravasation of the uterine sinuses and iliac vein, followed by pulmonary embolism, occurred where the fractional method of hysterosalpingography was performed. They intimate that complications occurred despite the ordinary precautions involved in careful fractional hysterosalpingography. Careful study of Karshmer and Stein's case report will reveal that their technique was neither careful nor fractional in any true sense of the words.

They state, "A hysterosalpingography was done in Dr. R.'s office by the fractional method. Two c.c. of Iodochlorol were injected, with x-ray exposure and visualization of the plate before a subsequent 2 c.c. portion was again injected. The right tube was not visualized even after the injection of 6 c.c. of dye. Since a considerable portion of the oil had leaked back into the vagina, a 5 c.c. portion of Iodochlorol and/or Lipiodol was injected under possibly increased pressure in an attempt either to fill the right tube or force it open."

Anatomists have long realized that the uterine cavity is not a true cavity in the nulliparous woman. It is only a potential cavity with a narrow slitlike concavity. My recent studies of the uterine cavities of 739 nulliparous women (this JOURNAL)[5] showed that the average capacity of such uteri was but 1.7 c.c. of iodized oil. The possible trauma resulting from the use of excessive amounts of iodized oil in hysterosalpingography was pointed out. I should like to state at this time that any injection of iodized oil into a nulliparous uterus, in amounts greater than 2 c.c. without the benefit of fluoroscopy and manometric and pressure control, may be dangerous.

Karshmer and Stein frankly state that after 6 c.c. of oil failed to reveal right tubal filling, and because some oil leaked from the cervix, another 5 c.c. of oil were instilled under "possibly increased pressure." These workers make no mention of the use of any manometer or apparatus to control the pressures used in the uterus. I should like to know what they mean by "possibly increased pressure." The pressure exerted in the uterus must have been

well over the danger zone of 200 mm. of mercury which is the limit accepted by authorities in this country. How else can they explain the entrance of the opaque medium into the uterine sinuses, hypogastric vein, and iliac vein? If fractional hysterosalpingography means the blind injection of an additional 5 c.c. of a foreign material into a uterus already so filled with oil that leakage and back-flow had occurred into the vagina, then we must change our terminology; certainly this was not any instance of fractional instillation, it was rather a massive instillation before the final x-ray was exposed.

It is no wonder then, after injection of about 11 c.c. of material under increased pressure into a uterus which normally will retain about 2 c.c. of oil, that intravasation and embolic phenomena took place. Far too much medium and far too much pressure had been used!

As I have pointed out again and again,[6, 7, 8] there is no excuse today for the physician who does not employ every available safeguard in the performance of hysterosalpingography. Manometric devices for use with fluoroscopy and hysterography were made available by Jarcho[9] and Béclère[10] twenty years ago. It was to avoid such complications as Karshmer and Stein report that I designed the Gynograph for use by both gynecologist and radiologist. So safe and controlled is this simple apparatus that the Council on Physical Medicine of the American Medical Association voted it as "acceptable" soon after this new gynoroentgenologic apparatus was described in the literature.[8, 11, 12] I am pleased to report that within the last fifteen years since using Jarcho's Pressometer, Béclère's Hysterometer, and finally my own Gynograph, I have never caused a uterine intravasation or embolism in 2,800 consecutive hysterosalpingographies.

Can it be that some physicians are unaware of the need for mechanical controls over pressure and volume in hysterosalpingography? It hardly seems likely. Endless numbers of papers appear with regularity appealing for controls and fluoroscopy in uterotubal radiology. Studies with the Gynograph, for example, have already appeared not only in this JOURNAL,[8] but have been published in *Fertility and Sterility*,[13] in *Radiology*,[14] and in the *Journal of the American Medical Association* under the reports of the Council on Physical Medicine.[11, 12]

Unfortunately, all that we believers in modern hysterosalpingography can do is to call the attention of our colleagues to reliable safeguards and urge their usage; we cannot force anyone to use them. Perhaps the case report of Karshmer and Stein, and their near fatality will do more to impress upon us that there is need for the exercise of greater care in hysterosalpingography than dozens of papers that any one of us could try to have published to point out such hazards.

ABNER I. WEISMAN, M.D.

1160 FIFTH AVENUE
NEW YORK, N. Y.
MARCH 9, 1951

References

1. Karshmer, N., and Stein, W.: AM. J. OBST. & GYNEC. 61: 458, 1951.
2. Ingersoll, F. M., and Robbins, L. L.: AM. J. OBST. & GYNEC. 53: 307, 1947.
3. Titus, P.: AM. J. OBST. & GYNEC. 53: 1067, 1947.
4. Weisman, A. I.: AM. J. OBST. & GYNEC. 54: 902, 1947.
5. Weisman, A. I.: AM. J. OBST. & GYNEC. 61: 202, 1951.
6. Weisman, A. I.: A New Technic in Uterotubal X-rays in the Diagnosis of Female Sterility. A motion picture exhibit before the Annual Session of the American Medical Association, Chicago, Ill., June, 1944.
7. Weisman, A. I.: Trans. Am. Soc. Study Steril. 2: 40, 1947.
8. Weisman, A. I.: AM. J. OBST. & GYNEC. 54: 145, 1947.
9. Jarcho, J.: Gynecological Roentgenology, New York, 1931, Paul B. Hoeber, Inc.
10. Béclère, C.: La Permeabilité et les obturations tubaires, Paris, 1929, Masson et Cie.
11. Council on Physical Medicine: J. A. M. A. 137: 1384, 1948.
12. Council on Physical Medicine: J. A. M. A. 142: 181, 1950.
13. Weisman, A. I.: Fertil. & Steril. 1: 321, 1950.
14. Weisman, A. I.: Radiology, January, 1951.

Reply by Dr. Karshmer

To the Editor:

I should like to relieve Dr. Stein of any of the burden of this criticism for he came into this case after the "damage" was already done. He simply managed the subsequent medical aspects of the case.

When it comes to hysterosalpingography, Dr. Weisman is truly a "crusader." I agree with him in his contention that hysterosalpingography is and should be a safe procedure. It has been such in my hands until this case occurred.

Dr. Weisman's criticism is welcome and for the greater part very well taken. However, I believe, in his enthusiasm, he has been entirely too severe in his criticism without being familiar with all the details of this particular case. I take this opportunity to enlighten him and others who might be similarly disposed to criticize. Certainly, I left myself wide open to criticism in this case report and welcome it if it will direct attention to the likelihood of this mishap.

To begin with, this patient was at no time a "near fatality." She ran a most uneventful course during her stay in the hospital and at no time was considered to be seriously ill. I am sure that many such "accidents" have occurred to others either without recognition or with belated recognition. These patients have undoubtedly been allowed to go on their way without any untoward effects. In a detailed article to appear in a forthcoming issue of the *New Jersey State Medical Journal* by Dr. Stein and myself on this subject, references are given to the literature concerning such cases.

I believe that Dr. Weisman is wrong in assuming that a total of 11 c.c. of opaque material was present because an x-ray taken just before the injection of the final 5 c.c. portion showed that the uterus was empty with all the oil in the vagina. While I have no proof of the actual pressure used, I doubt that it was 200 mg. or higher, as Dr. Weisman contends. I have a Kidde tubal insufflator which I use in all my cases and have acquired some notion of the pressure used. Unfortunately, for one reason or another, I failed to use it in this case.

In our more complete article mentioned above, the only fatal case that I could find was one in which the opaque material was injected at 80 mm.[1] which is assuredly a safe enough pressure to use. Sicard and Forestier[2] injected 2 to 4 c.c. of iodized oil directly into the veins of human subjects, with dyspnea as the only untoward symptom noted by the patient. I doubt whether that amount of oil ever entered the circulation of the patient reported by us. No evidence of iodides in the urine or actual oil emboli reaching the lungs could be discovered in our case which would further substantiate this contention.

Dr. Weisman is undoubtedly quite familiar with the literature on this subject. However, I should like to mention that several cases have been reported where oil was seen in the venous plexus of the uterine and ovarian veins after only 2 c.c. of material were injected.[3] There are also cases recorded where both tubes were immediately patent with opaque material in the peritoneal cavity at the same moment that oil embolism had already occurred.[4] These facts will tend to remove some of the onus of "far too much medium and far too much pressure has been used," for it has undoubtedly happened to others who may have been "more careful and fractional" in their technique than I was.

I should like to end this letter in a happy vein by reporting that this patient is now pregnant and should have had her baby by the time this matter is published. May we be bold enough to assume that the manipulation played a small part in overcoming her primary infertility of four years' duration by "forcibly" opening her tube or tubes?

NATHAN KARSHMER, M.D.

92 CARROLL PLACE
NEW BRUNSWICK, N. J.
MARCH 23, 1951

References

1. Gajzago, E.: Zentralbl. f. Gynäk. 53: 307, 1941.
2. Sicard, J. A., and Forestier, G.: Cited by Ingersoll and Robbins.[3]
3. Ingersoll, Francis M., and Robbins, Laurence L.: AM. J. OBST. & GYNEC. 53: 307, 1941.
4. Lin, Y. Y., and Tsou, S. H.: Chinese M. J. 49: 1241, 1935.
5. Witner, E., Cushman, H. P., and Leucutia, T.: Am. J. Roentgenol. 23: 125, 1930.

Item

Diplomates

The following candidates were certified by the American Board of Obstetrics and Gynecology after the examinations conducted in New York City, May 16, 1951.

Abrams, Herbert	226 Central St.	Lowell, Mass.
Ahearn, Robert E.	35 Riverside Dr.	Binghamton, N. Y.
Alessi, Silvio A.	11 E. Chase St.	Baltimore, Md.
Allen, Melvin A.	3701 Grandel Sq.	St. Louis, Mo.
Andrews, Herbert J.	1441 Westwood Blvd.	W. Los Angeles, Calif.
Anspaugh, Robert D.	504 Osler Bldg.	Oklahoma City, Okla.
Atkins, Harry T.	2500 Melrose Ave.	Cincinnati, Ohio
Aussprung, Harry L.	5742 N. Fifth St.	Philadelphia, Pa.
Bachman, Lyle	1136 Union St.	Honolulu, Hawaii
Barr, Samuel S.	255 S. 17th St.	Philadelphia, Pa.
Barrett, Scott R.	1409 N. Euclid Ave.	St. Louis, Mo.
Beacham, Daniel W.	1201 National Bank of Commerce Bldg.	New Orleans, La.
Bennett, Thomas R., Jr.	3620 Fairmount St.	Dallas, Texas
Benzon, George H., III	Lansdale Clinic	Landsdale, Pa.
Bianco, John J.	318 Cooper St.	Camden, N. J.
Bickerstaff, Hugh J.	Medical Arts Bldg.	Columbus, Ga.
Block, Robert E.	1474 President St.	Brooklyn, N. Y.
Boog, Janet M.	281 Haverhill St.	Lawrence, Mass.
Boyd, Harvey C.	13 Glenwood Ave., Nyanza Park	Tacoma, Wash.
Boyers, L. Morgan	1127 Eleventh St.	Sacramento, Calif.
Boysen, Theophilus H., III	812 S. George St.	York, Pa.
Brown, John B.	532 Arch Pl.	Glendale, Calif.
Brucato, Salvatore J.	30-65 Thirty-sixth St.	Astoria, L. I., N. Y.
Burnett, John E., Jr.	107 N. Fountain Ave.	Springfield, Ohio
Caldwell, Jesse B., Jr.	212 Realty Bldg.	Gastonia, N. C.
Callagan, Dwight A.	N. O. B., Guantanamo Bay, Cuba	c/o F. P. O., New York
Callahan, Justin T.	106 E. 79th St.	New York City
Cameron, Harold B.	423 S. Broadway St.	Tyler, Texas
Chatham, Beverly C.	620 Choctaw Ave.	Chickasha, Okla.
Cline, Wade M.	2205 Highland Ave.	Birmingham, Ala.
Collins, James I.	902 Stockdale	Flint, Mich.
Collins, Mary E.	309 Santa Monica Blvd.	Santa Monica, Calif.
Cook, James A.	1860 Ford Ave.	Wyandotte, Mich.
Cronlund, Raymond W.	230 N. Broad St.	Philadelphia, Pa.
Curtis, Lindsay R.	2279 Jackson Ave.	Ogden, Utah
Dantuono, Louise M.	10 W. 95th St.	New York City
Davidson, Vanda A., Jr.	3207 Turtle Creek	Dallas, Texas
Davis, George H.	6 E. Read St.	Baltimore, Md.
Davis, William L.	87 29th St.	Newport News, Va.
Deckert, William A.	1114 St. Paul St.	Baltimore, Md.
Dedman, Harold E.	310 Idaho St.	Boise, Idaho
Dees-Porch, Frances	152 Barrington Rd.	Upper Darby, Pa.
Delson, Barnet	1060 Ocean Ave.	Brooklyn, N. Y.
deMailly, Robert G.	2000 Van Ness Ave.	San Francisco, Calif.
Depp, Oren R.	914 Canal Bldg.	New Orleans, La.
DeVoe, Robert W.	3115 Webster St.	Oakland, Calif.
Diamond, Bernard	61 Eastern Parkway	Brooklyn, N. Y.
Doering, Wendell R.	968 Fisher Bldg.	Detroit, Mich.
Donald, Howard A.	1717 N Street, N. W.	Washington, D. C.
Donovan, Richard S.	968 Fisher Bldg.	Detroit, Mich.
Doyle, Richard J.	387 Essex St.	Salem, Mass.
Duffy, Leo T.	683 Asylum Ave.	Hartford, Conn.
Duggan, Eugene R.	16 N. Goodman St.	Rochester, N. Y.

Durfee, Raphael B.	2000 Van Ness Ave.	San Francisco, Calif.
Eccleston, Herbert H.	124 Elm Ave.	Hackensack, N. J.
Eisenstein, Morris I.	350 Central Park West	New York City
Englehart, Ferdinand K. (Single certification in gynecology only.)	701 Stuyvesant Ave.	Trenton, N. J.
Fain Irving	155 Chancellor Ave.	Newark, N. J.
Fallon, Walter R.	1501 East 67th St.	Chicago, Ill.
Farber, Emanuel P.	322 S. 16th St.	Philadelphia, Pa.
Farney, Jacob P.	6305 Brookside Plaza	Kansas City, Mo.
Farris, Joseph A.	2303 Government St.	Baton Rouge, La.
Feinstein, Harold	963 Madison Ave.	Memphis, Tenn.
Ferguson, Hal	2930 12th Ave., N.	Birmingham, Ala.
Fernandez-Fuster, Manuel	1803 Ponce de Leon Ave.	Santurce, Puerto Rico
Finn, Joseph W.	628 59th St.	Brooklyn, N. Y.
Fletcher, Thomas B., Jr.	516 N. Adams St.	Tallahassee, Fla.
Fontaine, William C.	870 Humboldt Parkway	Buffalo, N. Y.
Footer, Marvin P.	1835 I St., N. W.	Washington, D. C.
Franklin, H. Charles	10754 15th St., N. E.	Seattle, Wash.
Frech, Henry C.	Base Hospital, Sewart Air Force Base	Smyrna, Tenn.
Freed, Charles R.	1809 E. 18th Ave.	Denver, Colo.
Gamble, John J.	634 Madison Ave.	Albany, N. Y.
Ganser, Howard I.	1525 E. 53rd St.	Chicago, Ill.
Garabedian, Noubar J.	924 President St.	Brooklyn, N. Y.
Garber, Jesse G.	450 N. Bedford Dr.	Beverly Hills, Calif.
Garnet, James D.	330 S. 9th St.	Philadelphia, Pa.
Garnett, Alfred R.	746 Graydon Ave.	Norfolk, Va.
Gasser, George W.	3 N. Main	Logan, Utah
Gillespie, Robert H.	18 4th St., N. W.	Atlanta, Ga.
Gleeson, George L.	1107 N. Second St.	Harrisburg, Pa.
Goldcamp, Joseph H.	2508 Auburn Ave.	Cincinnati, Ohio
Gollin, Harvey A.	55 E. Washington St.	Chicago, Ill.
Gordon, Jacob M.	4623 N. Broad St.	Philadelphia, Pa.
Gottleib, Morris	1616 Pacific Ave.	Atlantic City, N. J.
Graves, James H.	113 E. Williams St.	Owosso, Mich.
Greene, Robert B.	4212 N. E. Broadway	Portland, Ore.
Griffin, Robert J.	203 W. Second St.	Lexington, Ky.
Grossblatt, Philip	31 Lincoln Park	Newark, N. J.
Haberlein, Charles R.	123½ E. Front St.	Traverse City, Mich.
Hardman, Edward F.	412 N. Church St.	Charlotte, N. C.
Harrison, Harold	Madigan Army Hospital	Tacoma, Wash.
Harryman, James E.	292 W. Western Ave.	Muskegon, Mich.
Hartford, Walter K.	1007 Medical Arts Bldg.	Oklahoma City, Okla.
Healy, Joseph J., Jr.	74 Ascan Ave.	Forest Hills, L. I., N. Y.
Heaton, Stuart C.	136 E. 64th St.	New York City
Hecker, Robert C.	3016 Nichols Ave., S. E.	Washington, D. C.
Hess, Catherine B.	3422 Midvale Ave.	Philadelphia, Pa.
Hinman, Crawford H.	221 Longwood Ave.	Boston, Mass.
Hodge, David F.	900 17th St.	Washington, D. C.
Hodnette, Frank B.	24 W. Chase St.	Pensacola, Fla.
Hoffman, Kathryn E.	635 Schofield Bldg.	Cleveland, Ohio
Hogans, Clarence W.	1902 7th Ave.	New York City
Huey, Thomas W., Jr.	117 W. 7th Street	Charlotte, N. C.
Hughes, Charles R., Jr.	1801 K St., N. W.	Washington, D. C.
Huston, J. Wilson	U. S. Naval Hospital	Key West, Fla.
Ingalls, Edgar G.	313 Medical Arts Bldg.	Minneapolis, Minn.
Isham, Charles A.	1540 6th Ave.	San Diego, Calif.
Jack, William W.	Blodgett Medical Bldg.	Grand Rapids, Mich.
James, Walter F. B.	Hubbard Hospital	Nashville, Tenn.
Jarvis, Garth L.	University of Texas Medical Branch	Galveston, Texas
Jennett, Raymond J.	543 E. McDowell Rd.	Phoenix, Ariz.
Johnson, Herbert F.	42 S. Woodland Ave.	Woodbury, N. J.
Jones, William J.	699 E. South Temple St.	Salt Lake City, Utah
Jordan, Harry J.	409 North Ave.	Pittsburgh, Pa.
Jordan, John R.	6315 Prospect Ave.	Dallas, Texas
Karberg, Richard J.	420 Columbia St.	Lafayette, Ind.
Kautsky, Karl	440 West End Ave.	New York City

Keller, Michael L.	673 E. 27th St.	Paterson, N. J.
Kerner, John A.	2107 Van Ness Ave.	San Francisco, Calif.
Kitzmiller, John L.	3001 W. Grand Blvd.	Detroit, Mich.
Knorr, John K. (III)	2216 Delancey Pl.	Philadelphia, Pa.
Kodesh, Jack B.	Magdalena Esqu. Washington	Santurce, Puerto Rico
Kohl, Mathias F. F.	206 S. Main St.	Rockford, Ill.
Kohl, Schuyler G.	Kings County Hospital	Brooklyn, N. Y.
Kramer, Elmer E.	530 E. 70th St.	New York City
Kron, William L.	15 Hillside Ave.	Roslyn Heights, N. Y.
Kuhn, John J.	2431 K St., N. W.	Washington, D. C.
Lang, Warren R.	255 S 17th St.	Philadelphia, Pa.
Lavorgna, Michael H.	146 Sherman Ave.	New Haven, Conn.
Lawrence, N. Berwyn	1138 N. "D" St.	San Bernardino, Calif.
Leibold, Robert W.	Wheeling Clinic	Wheeling, W. Va.
Leighton, Herbert T.	319 Longwood Ave.	Boston, Mass.
Long, Wilmer N.	11 E. Chase St.	Baltimore, Md.
Lord, Robert N.	1480 Elm St.	Manchester, N. H.
Luders, John A.	6013 Greene St.	Germantown, Pa.
Lukeman, Hermann J.	U. S. Naval Hospital	Portsmouth, N. H.
Lyon, Edward, Jr.	416 Pine St.	Williamsport, Pa.
Magoon, Leslie B.	680 S. 15th St.	San Jose, Calif.
Mandelbaum, Carl C.	133 E. 58th St.	New York City
Mangone, Edith K.	74 Bentley Ave.	Jersey City, N. J.
Martin, Ronald F.	505 Sixth St.	Sioux City, Iowa
Mastellone, George J.	164 Clinton St.	Brooklyn, N. Y.
Masters, William H.	630 S. Kingshighway Blvd.	St. Louis, Mo.
Matheke, George	555 William St.	East Orange, N. J.
McClusky, Donald K.	340 Main St.	Worcester, Mass.
McFadden, Francis R.	111 E. Third St.	Davenport, Iowa
McGowan, Gordon W.	31 S. W. Court Ave.	Pendleton, Ore.
Melchior, George W.	400 W. Nash St.	Wilson, N. C.
Meltzer, Hyman J.	1550 E. 53rd St.	Chicago, Ill.
Merendino, Vincent J.	521 Park Ave.	New York City
Mernit, Arthur H.	43-06 Bell Blvd.	Bayside, N. Y.
Merritt, Julius M.	1930 Wilshire Blvd.	Los Angeles, Calif.
Miller, Richard E.	242 E. Broad St.	Tamaqua, Pa.
Millikan, William J.	3736 N. Delaware St.	Indianapolis, Ind.
Mitchell, William A.	3724 Oneal St.	Greenville, Tex.
Modisher, Melvin W.	350 W. 10th St.	Erie, Pa.
Moore, John G., Jr.	University Hospitals	Iowa City, Iowa
Nadler, Arthur A.	947 W. 8th St.	Los Angeles, Calif.
Napp, Emil E.	75 Central Park, West	New York City
Nash, Charles H., Jr.	Gallinger Municipal Hospital	Washington, D. C.
Nemrow, Curt M.	7016 Euclid Ave.	Cleveland, Ohio
Nolan, Bernard E.	932 Maccabees Bldg.	Detroit, Mich.
Novak, Edmund R.	Johns Hopkins Hospital	Baltimore, Md.
O'Neil, George J.	205 N. Main St.	Bloomington, Ill.
O'Rourke, James J.	40 E. 62nd St.	New York City
Panic, Stephen M.	3341 E. Davison Ave.	Detroit, Mich.
Parish, Frank M.	1506 S. Kuhl Ave.	Orlando, Fla.
Passmore, Glen G.	Nix Professional Bldg.	San Antonio, Texas
Paull, Thomas	118 Union Ave.	Framingham, Mass.
Peninger, Floyd L.	1513 Line Ave.	Shreveport, La.
Pereyra, Armand J.	U. S. Naval Hospital	Bremerton, Wash.
Peterson, Lowell F.	55 E. Washington St.	Chicago, Ill.
Pichette, J. Walton	15146 Michigan Ave.	Dearborn, Mich.
Pierce, Robert R.	116 William H. Taft Rd.	Cincinnati, Ohio
Podger, Kenneth A.	604 W. Chapel Hill St.	Durham, N. C.
Pontarelli, Domenic J.	5662 Miriam Rd.	Philadelphia, Pa.
Preston, Stephen N.	Western Montana Clinic	Missoula, Mont.
Pruit, Alton R.	406 N. Penn	Roswell, N. Mex.
Ranney, Brooks	Fourth St., and Park Ave.	Yankton, S. D.
Rasin, Carl	U. S. Army Hospital	Camp Pickett, Va.
Reed, Howard B.	122 Railroad St.	St. Johnsbury, Vt.
Reid, William A.	300 Thayer St.	Providence, R. I.
Rhind, Ralph	6242 W. Manchester Ave.	Los Angeles, Calif.
Roach, William R.	700 N. Michigan Ave.	Chicago, Ill.
Robertson, Alexander R., IV	106 Litchfield St.	Torrington, Conn.

Romeo, Zachary J.	124 18th St.	Rock Island, Ill.
Rubin, Harold W.	14 Charlesgate, West	Boston, Mass.
Rubin, Morris M.	U. S. Naval Hospital	Oakland, Calif.
Rubin, Samuel	803 Cathedral St.	Baltimore, Md.
Rutledge, Felix N.	4115 Fannin	Houston, Texas
Sanderson, Richard J.	407 Prospect St.	Beloit, Wis.
Sawtell, James H.	Richland Medical Center	Richland, Wash.
Scarito, Nina E.	95 Summer St.	Lawrence, Mass.
Schaupp, John B.	490 Post St.	San Francisco, Calif.
Schneider, Edward	2 Greenridge Ave.	White Plains, N. Y.
Schretzmann, Rudolph C.	135 State St.	Hackensack, N. J.
Schultz, John H.	261 Alexander St.	Rochester, N. Y.
Schwartz, Albert	191 Ocean Ave.	Brooklyn, N. Y.
Schweizer, Donald C.	153 Bishop St.	Greensboro, N. C.
Scorza, Aldo C.	417 Ocean Ave.	Brooklyn, N. Y.
Scott, Ronald R.	7021 Seville Ave.	Huntington Park, Calif.
See, William B.	Professional Bldg.	Columbia, Mo.
Seeger, Allen H.	920 Jefferson St.	Wilmington, Del.
Shnayerson, Edward F.	550 Ocean Ave.	Brooklyn, N. Y.
Silbermann, Eugene J.	521 Park Ave.	New York City
Simmons, Raymond J.	39 N. Goodman St.	Rochester, N. Y.
Skwerer, Arthur P.	36 Plaza St.	Brooklyn, N. Y.
Slivka, James E.	3850 Washington Park Blvd.	Cleveland, Ohio
Smale, Leroy E.	1304 Chester Ave.	Bakersfield, Calif.
Smith, James H.	1665 Madison Ave.	Memphis, Tenn.
Smith, Linwood	60 South 4th, E.	Salt Lake City, Utah
Snyder, Wesley J., Jr.	208 N. Sumter St.	Sumter, S. C.
Sproul, Alexander E.	Professional Bldg.	Staunton, Va.
Starcke, Sewell K.	1422 Euclid Ave.	Cleveland, Ohio
Stashak, Theodore S.	576 "B" Street	Santa Rosa, Calif.
Stevens, Robert W.	1116 Missouri Theatre Bldg.	St. Louis, Mo.
Stipp, Charles G.	1018 Summit Ave.	Seattle, Wash.
Suggs, Charles L., Jr.	204 Interstate Bldg.	Chattanooga, Tenn.
Swift, Leroy R.	1111 Fayetteville St.	Durham, N. C.
Tancer, M. Leon	1 East 68th St.	New York City
Taw, Richard L.	3450 W. 43rd St.	Los Angeles, Calif.
Teichner, Herbert	121 E. 31st St.	New York City
Tepper, Sidney M.	136 N. Fifth St.	El Centro, Calif.
Terman, Irving	114 E. 78th St.	New York City
Terrin, Alexander J.	652 Eastern Parkway	Brooklyn, N. Y.
Thebaut, William M., Jr.	350 29th St.	Oakland, Calif
Thom, Charles H.	6 East 79th St.	New York City
Threlkeld, L. Duncan	1220 N. Walker	Oklahoma City, Okla.
Tunney, Robert B.	115 E. Eager St.	Baltimore, Md.
Turner, Henry B.	30 S. Bellevue Bldg.	Memphis, Tenn.
Wainer, Amos S.	2031 Locust St.	Philadelphia, Pa.
Ward, George H.	947 W. Eighth St.	Los Angeles, Calif.
Ward, Simon V.	4414 Magnolia St.	New Orleans, La.
Watson, David F.	210 E. Coffee St.	Greenville, S. C.
Wayburn, Gates J.	1049 Fifth Ave.	Huntington, W. Va.
Weigle, Edward H.	7707 Fay Ave.	La Jolla, Calif.
Weinstein, Benjamin B.	1441 Delachaise St.	New Orleans, La.
(Single certification in gynecology only.)		
White, William H., Jr.	4500 Olive St.	St. Louis, Mo.
Wichser, Celeste G.	926 Melpomene Ave.	New Orleans, La.
Wilkinson, Hildegarde	334 N. Central Ave.	Glendale, Calif.
Williams, Edwin L.	2106 West End Ave.	Nashville, Tenn.
Willson, Prentiss, Jr.	1717 N Street, N. W.	Washington, D. C.
Wilson, Robert N., Jr.	Suburban Bldg.	Ardmore, Pa.
Woolsey, Elwood L.	U. S. Naval Hospital	Memphis, Tenn.
Worsham, John W.	1400 McCullough St.	San Antonio, Texas
Wortmann, Robert F.	510 Professional Bldg.	Kansas City, Mo.
Wyatt, Clarence A., Jr.	1133 Punchbowl St.	Honolulu, Hawaii

PAUL TITUS, M.D., Pittsburgh, Pa.
Secretary-Treasurer,
American Board of Obstetrics and Gynecology

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Walter T. Dannreuther, New York. *Secretary,* John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Next meeting, Hot Springs, Va., May 12, 13, and 14, 1952.

American Association of Obtetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* James K. Quigley, Rochester, N. Y. *Secretary,* William F. Mengert, 2211 Oak Lawn Ave., Dallas 4, Texas. Annual meeting Hot Springs, Va., September 6, 7, and 8, 1951.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Russell J. Moe, Duluth, Minn. *Secretary-Treasurer,* Harold L. Gainey, 116 S. Michigan Ave., Chicago 3, Ill. Annual meeting to be held in September, 1951.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* E. D. Colvin, Atlanta, Ga. *Secretary-Treasurer,* John C. Burwell, Jr., 416 Jefferson Bldg., Greensboro, N. C.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Arthur B. Hunt, Rochester, Minn. *Secretary,* Bernard J. Hanley, 1930 Wilshire Blvd., Los Angeles, Calif. Annual meeting, Chicago, Ill., June 9-13, 1952.

New York Obstetrical Society. (1863) *President,* Howard C. Taylor, Jr. *Secretary,* Charles M. McLane, 960 Park Ave., New York 28, N. Y. Second Tuesday, from October to May.

Obstetrical Society of Philadelphia. (1868) *President,* James P. Lewis. *Secretary,* George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* M. Edward Davis. *Secretary,* Edwin J. De Costa, 720 S. Michigan Ave., Chicago 3, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* Martin Shir. *Secretary,* J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. Third Wednesday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn. N. Y.

The Obstetrical and Gynecological Society of Maryland. (1929) *President,* Emil Novak. *Secretary-Treasurer,* W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Joseph G. Crotty. *Secretary,* Robert R. Pierce, 116 William Howard Taft Road, Cincinnati 19, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Rudy F. Vogt. *Secretary-Treasurer,* Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. President, William Sharkey. *Secretary-Treasurer,* Jack W. Dowsett, 1020 S. W. Taylor St., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* Eugene A. Conti. *Secretary-Treasurer,* David Katz, 103 Century Bldg., Pittsburgh 22, Pa. Meetings, first Monday of each month, October to May.

Obstetrical Society of Boston. (1861) *President,* Roy J. Heffernan. *Secretary,* Francis Rouillard, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16. Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Roy E. Fallas, Los Angeles, Calif. *Secretary-Treasurer,* Donald G. Tollefson, 511 South Bonnie Brae St., Los Angeles 5, Calif.

Washington Gynecological Society. (1933) *President,* J. Bay Jacobs. *Secretary,* Allan E. King, 915 19 Street, N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Harry Meyer. *Secretary,* Abe Golden, 1430 Tulane Ave., New Orleans 12, La. Meetings held October, November, January, March, and May.

St. Louis Gynecological Society. (1924) *President,* Paul Fletcher. *Secretary,* J. Russell Vaughan, 634 North Grand Blvd., St. Louis 3, Mo., Regular meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Donald Dallas. *Secretary,* Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* S. Foster Moore. *Secretary-Treasurer,* Carey Hiett, 603 College Avenue, Fort Worth 4, Texas.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* O. W. Picard. *Secretary,* Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Nathan N. Cohen. *Secretary,* Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. (1940) *President,* M. Y. Dabney. *Secretary,* Buford Word, 929 South Twentieth Street, Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Robert K. Plant. *Secretary-Treasurer,* Gerald F. Thomas, 1427 Medical and Dental Bldg., Seattle 1, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.

Denver Gynecological and Obstetrical Society. (1942) *President,* Edward L. Harvey. *Secretary-Treasurer,* Jack M. Simmons, Jr., 804 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* J. W. Prentice. *Secretary-Treasurer,* Alice D. Watts, 324 East Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* Clyde R. Kennedy. *Secretary-Treasurer,* John F. Wanless, 2001 Fourth Ave., San Diego 1, Calif. Meetings held on the last Friday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* W. H. Gilsdorf, Valley City. *Secretary-Treasurer,* C. B. Darner, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* John M. Nokes. *Secretary,* Chester D. Bradley, 2914 West Avenue, Newport News, Va. Meetings held in April and October.

Columbus Obstetric-Gynecologic Society. (1944) *President,* Rov Krigbaum. *Secretary,* Zeph J. R. Hollenbeck, 40 South Third St., Columbus, Ohio. Meetings held last Wednesday of each month from September to May.

Naussau Obstetrical Society. (1944) *President,* Robert S. Millen. *Secretary-Treasurer,* Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Milton D. Klein. *Secretary.* Alex Charlton, 1749 Grand Concourse, New York 53, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* E. Gerald Layton. *Secretary-Treasurer,* L. Bruce Donaldson, 805 Medical and Dental Bldg., Seattle 1, Wash. Next meeting to be held Sept. 8, 1951, Washington Athletic Club, Seattle.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Kenneth E. Cox. *Secretary,* James E. Keeler, 4301 Main St., Kansas City, Mo. Meetings last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* Gordon Rosenblum. *Secretary-Treasurer,* A. N. Webb, 3130 W. 6th St., Los Angeles 5, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* F. Bayard Carter. *Secretary,* Richard L. Pearse, 604 W. Chapel Hill St., Durham, N. C. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* H. B. Atlee. *Secretary,* K. M. Grant. Annual meeting, June, 1950.

Akron Obstetrical and Gynecological Society. (1946) *President,* Alven M. Weil. *Secretary-Treasurer,* Robert M. DeWitt. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio Bldg.

Minnesota Obstetrical and Gynecological Society. *President,* William F. Mercil. *Secretary-Treasurer,* Rodney F. Sturley, 350 Saint Peter St., St. Paul, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* John D. Milton. *Secretary,* Richard F. Stover, 701 duPont Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Ralph Luikhart. *Secretary-Treasurer,* Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* John W. Records. *Secretary-Treasurer,* Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.

Cleveland Obstetrical and Gynecological Society. (1947) *President,* J. L. Reycraft. *Secretary,* G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* Raymond T. Potter. *Secretary,* Felix H. Vann, 242 Engle St., Englewood, N. J. Meetings semiannually.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* Guy C. Milnor. *Secretary,* Rodney T. West, The Clinic, Honolulu 14, T. H. Meetings third Monday of each month, Mabel Smyth Building.

Oregon Society of Obstetricians and Gynecologists. *President,* Gerald Kinzel. *Secretary-Treasurer,* Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.

National Federation of Obstetric-Gynecologic Societies. (1945) *President,* Ralph E. Campbell. *Secretary,* Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.

Dayton Obstetrical and Gynecological Society. (1937) *President,* C. E. Mumma. *Secretary,* N. J. Thompson, 610 Harries Bldg., Dayton 2, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.

Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President,* C. P. Hawkins. *Secretary,* Oran V. Prejean, 4317 Oak Lawn Ave., Dallas, Texas. Meetings in spring and fall.

Queens Gynecological Society. (1948) *President,* James, V. Rizzi. *Secretary,* George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.

Mississippi Association of Obstetricians and Gynecologists. (1947) *President,* John F. Lucas, Greenwood, Miss. *Secretary-Treasurer,* Claude G. Callender, 727 Carlisle St., Jackson 2, Miss. Meetings held semiannually.

Florida Obstetric and Gynecologic Society. (1948) *President,* Robert G. Spicer. *Secretary-Treasurer,* Dorothy D. Brame, 1235 Kuhl Ave., Orlando, Fla. Next annual meeting, April, 1951, at Hollywood, Fla.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* J. Decherd Guess. *Secretary,* Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* W. Herbert Burwig. *Secretary,* Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.

El Paso Gynecological Society. (1948) *President,* C. C. Boehler. *Secretary-Treasurer,* Robert J. Cardwell, 414 Banner Bldg., El Paso, Texas.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* Clyde Sparks, Ashland, Ky. *Secretary-Treasurer,* J. B. Marshall, Louisville, Ky.

Indianapolis Obstetrical and Gynecological Society. (1947) *President,* Gerald W. Gustafson. *Secretary-Treasurer,* C. O. McCormick, Jr., 621 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.

Houston Obstetrical and Gynecological Society. (1939) *President,* Arthur Faris. *Secretary-Treasurer,* J. T. Armstrong, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.

Iowa Obstetric and Gynecologic Society. *President,* J. H. Randall. *Secretary,* William C. Keettel, Iowa City, Iowa.

Memphis Obstetrical and Gynecological Society. (1950) *President,* Phil C. Schreier. *Secretary,* James H. Smith, 1665 Madison Ave., Memphis 4, Tenn. Meetings, fourth Friday, October to May.

Birmingham Obstetrical and Gynecological Society. (1949) *President,* W. N. Jones. *Secretary,* Herbert H. Thomas, 1005 South Twenty-First St., Birmingham, Ala. Meetings four times yearly.

Mobile Obstetrical and Gynecological Society. (1949) *President,* John C. Hope, Jr. *Secretary,* Virginia E. Webb, 1322 Springhill Ave., Mobile, Ala. Meetings held second Thursday of January, April, July, and October.

Utah Obstetrical and Gynecological Society. (1948) *President,* William M. Nebeker. *Secretary,* Vernal H. Johnson, 2279 Jackson Ave., Ogden, Utah. Meetings held second Thursday of October, December, March, and May, at the University Club, Salt Lake City.

Inter-urban Obstetrical and Gynecological Society. (1949) *President,* D. E. Cannell. *Secretary,* E. R. Duggan, 16 North Goodman St., Rochester 7, N. Y. Next meeting will be held in Toronto, October, 1951.

New Mexico Obstetrical and Gynecological Society. (1947) *President,* Louis McRae. *Secretary-Treasurer,* LeRoy J. Bowers, Lovelace Clinic, Ridgecrest Drive and Gibson Ave., Albuquerque, N. Mex. Meetings held third Thursday in March, June, September, and December.

Pacific Northwest Obstetrical and Gynecological Association. (1947) *President,* Frank L. MacPhail. *Secretary,* Richard D. Reekie, W. 407 Riverside Ave., Spokane 8, Wash. Next annual meeting, June 25-28, 1952, Many Glaciers Hotel, Glacier Park, Montana.